

P20670

TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371U.S. APPLICATION NO. (If known, see 37 CFR  
1.5)

09/763617

INTERNATIONAL APPLICATION NO.

PCT/EP99/06486

INTERNATIONAL FILING DATE

3 September 1999

PRIORITY DATE CLAIMED

5 September 1998

TITLE OF INVENTION

GABA UPTAKE INHIBITORS HAVING A PYRROLIDINE STRUCTURE

APPLICANT(S) FOR DO/EO/US

Klaus WANNER, Günther FÜLEP, and Georg HÖFNER

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. ☒ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a. ☒ is attached hereto (required only if not communicated by the International Bureau).
  - b. ☒ has been communicated by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
  - b. ☐ have been communicated by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3))
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).  
"Unexecuted"
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (U.S.C. 371(c)(5)).

**Items 11 to 16 below concern other document(s) or information included:**

11. Assignee: BDD BEROLINA DRUG DEVELOPMENT AB of Svedala, SWEDEN
12. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
13. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
14. ☒ A FIRST preliminary amendment.  
☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ Figure of Drawing to be published \_\_\_\_\_
18. ☒ Other items or information:  
Cover Sheet and International Application as published in German.  
Cover Letter under 35 USC 371 and 1.495.  
Claim of Priority.

APPLICATION NO. (If known, see 37 CFR 1.57) <b>09/763617</b>		INTERNATIONAL APPLICATION NO. PCT/EP99/06486		ATTORNEY'S DOCKET NUMBER P20670	
19. The following fees are submitted:  Basic National Fee (37 CFR 1.492(a)(1)-(5)):  Search report has been prepared by the EPO or JPO. . . . . \$ 860.00  International preliminary examination fee paid to USPTO (37 CFR 1.482). . . . . \$ 690.00  No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO(37 CFR 1.445(a)(2)). . . . . \$ 710.00  Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO. . . . . \$1,000.00  International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4). . . . . \$ 100.00  ENTER APPROPRIATE BASIC FEE AMOUNT =				CALCULATIONS	PTO USE ONLY
				\$860.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than 20 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
Claims	Number Filed	Number Extra	RATE		
Total Claims	15 - 20 =	0	X \$18.00	\$0.00	
Independent Claims	1 - 3 =	0	X \$80.00	\$0.00	
Multiple dependent claim(s) (if applicable)			+ \$270.00	\$0.00	
TOTAL OF ABOVE CALCULATIONS =				\$860.00	
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				\$430.00	
SUBTOTAL =				\$430.00	
Processing fee of \$130.00 for furnishing the English translation later than 20 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+	
Extension of Time fee in the amount of \$					
TOTAL NATIONAL FEE =				\$430.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				+	
TOTAL FEES ENCLOSED =				\$430.00	
				Amount to be refunded	\$
				Charged	\$
<p>a. <input checked="" type="checkbox"/> A check in the amount of \$430.00 to cover the above fees is enclosed.</p> <p>b. Please charge my Deposit Account No. _____ in the amount of \$_____ to cover the above fees.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0089.</p> <p>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.437(a) or (b)) must be filed and granted to restore the application to pending status.</p> <p>SEND ALL CORRESPONDENCE TO CUSTOMER NO. 7055 AT THE PRESENT ADDRESS OF: Neil F. Greenblum GREENBLUM &amp; BERNSTEIN, P.L.C. 1941 Roland Clarke Place Reston, VA 20191 (703) 716-1191</p>					
				SIGNATURE Neil F. Greenblum NAME 33.094 28.394 REGISTRATION NUMBER	

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PCT  
#  
JG19 Rec'd PCT/PTO 0 4 JUN 2001

Attorney Docket No. 20670

In re application of : K. WANNER et al.  
Serial No. : 09/763,617

Box Non-Fee  
Group Art Unit:

Filed : September 3, 1999

Examiner:

For : GABA UPTAKE INHIBITORS HAVING A PYRROLIDINE STRUCTURE

THE COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

Sir:

Transmitted herewith is a Second Preliminary Amendment in the above-captioned application.

- \_\_\_ Small Entity Status of this application under 37 C.F.R. 1.9 and 1.27 has been established by a verified statement previously filed.  
\_\_\_ A verified statement to establish small entity status under 37 C.F.R. 1.9 and 1.27 is enclosed.  
☒ An Information Disclosure Statement, PTO Form 1449, and references cited.  
\_\_\_ No additional fee is required.

The fee has been calculated as shown below:

Claims After Amendment	No. Claims Previously Paid For	Present Extra	Small Entity		Other Than A Small Entity	
			Rate	Fee	Rate	Fee
Total Claims: 31	*20	11	x 9=	\$99.00	x 18=	\$0.00
Indep. Claims: 3	**3	0	x 40=	\$0.00	x 80=	\$0.00
Multiple Dependent Claims Presented			+135=	\$0.00	+270=	\$0.00
Extension Fees for Month				\$0.00		\$0.00
Total:				\$99.00	Total:	\$0.00

\*If less than 20, write 20

\*\*If less than 3, write 3

- \_\_\_ Please charge my Deposit Account No. 19-0089 in the amount of \$\_\_\_\_.  
☒ A Check in the amount of \$ 99.00 to cover the \*filing/extension\* fee is included.  
☒ The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 19-0089.  
☒ Any additional filing fees required under 37 C.F.R. 1.16.  
☒ Any patent application processing fees under 37 C.F.R. 1.17, including any required extension of time fees in any concurrent or future reply requiring a petition for extension of time for its timely submission (37 CFR 1.136)(a)(3).

06/07/2001 UEDUVIJE 00000062 09763617

01 FC:967

99.00 GF

Neil F. Greenblum  
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P20670.A02



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant :K. WANNER et al.

Serial No. : 09/763,617

Filed :September 3, 1999

For :GABA UPTAKE INHIBITORS HAVING A PYRROLIDINE STRUCTURE

**SECOND PRELIMINARY AMENDMENT**

Commissioner of Patents and Trademarks  
Washington, D.C. 20231

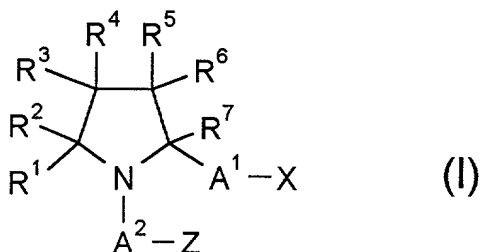
Sir:

Prior to the examination of the above-identified patent application, the Examiner is respectfully requested to amend the claims as follows:

IN THE CLAIMS

Please cancel claims 16-30 without prejudice or disclaimer. Please enter the following claims 31-61 for consideration by the Examiner:

---31. A compound of general formula (I)



wherein

$R^1$  to  $R^7$  are independently selected from H, optionally substituted  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl, optionally substituted aryl or heteroaryl, OH, halogen, CN,  $OR^{12}$ ,  $SR^{12}$ ,  $COR^{12}$ ,  $COOR^{12}$ ,  $SOR^{12}$ ,  $SO_2R^{12}$ ,  $NR^{13}R^{14}$ ,  $CONR^{13}R^{14}$ ,  $SO_2NR^{13}R^{14}$ , where  $R^{13}$  and  $R^{14}$  are independently selected from H and  $C_{1-3}$  alkyl and  $R^{12}$  represents  $C_{1-6}$  alkyl ; two of  $R^1$  to  $R^7$ , together with the atoms connecting them, each may form a 3- to 6-membered ring system, which ring system may contain one or more heteroatoms;  $R^1$  and  $R^2$  and/or  $R^3$  and  $R^4$  and/or  $R^5$  and  $R^6$  may be replaced by an optionally substituted alkylidene group or =O; and two of  $R^1$  to  $R^7$  which are positioned at adjacent carbon atoms may each be replaced by a C-C bond;

$A^1$  is selected from  $(-CR^8R^9)_n$ , optionally substituted  $C_{3-6}$  cycloalkylene and a combination of these groups,  $R^8$  and  $R^9$  being independently selected from H,  $C_{1-6}$  alkyl, halogen, OH,  $OR^{12}$  and  $NR^{13}R^{14}$  and where for  $n \geq 2$ ,  $R^8$  and  $R^9$  may be different in each group and two groups selected from  $R^8$  and  $R^9$  at adjacent C atoms may be replaced by a C-C bond, and a group -O- or -CO- may be positioned between two adjacent groups  $CR^8R^9$ ; and wherein one of  $R^8$  and  $R^9$  may be combined with one of  $R^1$  to  $R^7$  to form a 5- to 7-membered ring structure; and  $n = 0, 1, 2, 3$  or  $4$ ;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and pharmaceutically acceptable cations;

A<sup>2</sup> is  $(-CR^{10}R^{11})_m$ , where R<sup>10</sup> and R<sup>11</sup> are independently selected from H, C<sub>1-2</sub> alkyl and halogen; where for m ≥ 2 the groups R<sup>10</sup> and R<sup>11</sup> may be different in each group, a group -O- or -S- may be positioned between two adjacent groups -CR<sup>10</sup>R<sup>11</sup>-, and two groups selected from R<sup>10</sup> and R<sup>11</sup> at adjacent C atoms may be replaced by a C-C bond; and wherein one of R<sup>10</sup> and R<sup>11</sup> may be combined with one of R<sup>1</sup> to R<sup>9</sup> to form a 5- to 7-membered ring structure; and m is 1, 2, 3, or 4;

Z is selected from Y<sub>3</sub>C-O-, Y<sub>2</sub>C=CR<sup>15</sup>- and Y<sub>2</sub>C=N-O-, where R<sup>15</sup> is selected from H, C<sub>1-3</sub> alkyl or halogen and the groups Y are independently selected from optionally substituted C<sub>6-12</sub> aryl and optionally substituted C<sub>2-5</sub> heteroaryl having up to three heteroatoms independently selected from N, O and S, and the groups Y may be linked by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from -O-, -S-, -NH-, -O-, -CH=CH-, -CH=N-, -CH<sub>2</sub>- and -CH<sub>2</sub>CH<sub>2</sub>-;

as well as the individual stereoisomers of these compounds.

32. The compound of claim 31, wherein R<sup>7</sup> is hydrogen and R<sup>1</sup> to R<sup>6</sup> are independently selected from hydrogen, optionally substituted C<sub>1-3</sub> alkyl, halogen, OH, CN, optionally substituted phenyl and optionally substituted heteroaryl having 5 to 10 ring members and one or two heteroatoms selected from O, N and S.

33. The compound of claim 32, wherein R<sup>1</sup> to R<sup>6</sup> are independently selected from hydrogen, C<sub>1-3</sub> alkyl and phenyl.

34. The compound of claim 33, wherein all of  $R^1$  to  $R^7$  represent hydrogen.

35. The compound of claim 31, wherein  $A^1$  is  $(-CR^8R^9-)_n$ ,  $R^8$  and  $R^9$  are independently selected from H and  $C_{1-3}$  alkyl and n has a value of 1, 2 or 3.

36. The compound of claim 35, wherein  $R^8$  and  $R^9$  are each hydrogen and n has a value of 1 or 2.

37. The compound of claim 34, wherein X is COOM, with  $M = H, Na, K, NH_4, Ca_{0.5}$  or  $Mg_{0.5}$ .

38. The compound of claim 37, wherein X is selected from H and Na.

39. The compound of claim 31, wherein  $R^{10}$  and  $R^{11}$  are independently selected from H and  $C_{1-2}$  alkyl and m is 2 or 3.

40. The compound of claim 39, wherein  $R^{10}$  and  $R^{11}$  are each H and  $m = 2$ .

41. The compound of claim 35, wherein Z is  $Y_3C-O-$  and the groups Y are phenyl groups optionally substituted with one to two substituents selected from  $C_{1-3}$  alkoxy,  $C_{1-3}$  alkyl, halogen, OH,  $NO_2$ , CN and  $NR^{13}R^{14}$ .

42. The compound of claim 41, wherein the groups Y are identical and represent phenyl substituted with one C<sub>1-3</sub> alkoxy group.

43. The compound of claim 42, wherein the phenyl groups are para-substituted with a C<sub>1-2</sub> alkoxy group.

44. The compound of claim 31, wherein Z is Y<sub>2</sub>C=CR<sup>15</sup>-, the groups Y are selected from optionally substituted phenyl and optionally substituted heteroaryl having 5 to 6 ring members and one to two heteroatoms independently selected from O, N and S and R<sup>15</sup> is selected from H and CH<sub>3</sub>.

45. The compound of claim 44, wherein R<sup>15</sup> is H.

46. The compound of claim 45, wherein the groups Y carry 0, 1 or 2 substituents, the substituents being selected from C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy, halogen, OH, NO<sub>2</sub>, CN and NR<sup>13</sup>R<sup>14</sup>.

47. The compound of claim 44, wherein the groups Y are the same and are selected from phenyl, 4-methoxyphenyl and 3-methyl-2-thienyl.

48. The compound of claim 31, wherein Z is Y<sub>2</sub>C=N-O- and the groups Y are selected from optionally substituted phenyl and optionally substituted heteroaryl having 5 to 6 ring members and one to two heteroatoms independently selected from O, N and S.



49. The compound of claim 31, wherein

$R^1$  to  $R^7$  are independently selected from H,  $C_{1-3}$  alkyl and phenyl;

$A^1$  represents  $(-CR^8R^9-)_n$ ,  $R^8$  and  $R^9$  are independently selected from H and  $C_{1-3}$  alkyl, and  $n = 1$  or  $2$ ;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and Na;

$A^2$  is  $(-CR^{10}R^{11}-)_m$ , where  $R^{10}$  and  $R^{11}$  are independently selected from H and  $C_{1-2}$  alkyl and  $m$  is  $2$  or  $3$ ; and

Z is selected from  $Y_3C-O-$  and  $Y_2C=CR^{15}-$ ,  $R^{15}$  is selected from H and methyl and the groups Y are identical and selected from optionally substituted  $C_{6-12}$  aryl and optionally substituted  $C_{2-5}$  heteroaryl having up to three heteroatoms independently selected from N, O and S.

50. The compound of claim 49, wherein  $R^1$  to  $R^7$  are independently selected from H and methyl.

51. The compound of claim 50, wherein  $R^8$  and  $R^9$  are independently selected from H and methyl, and  $n = 1$ .

52. The compound of claim 49, wherein  $R^{10}$  and  $R^{11}$  are independently selected from H and  $C_{1-2}$  alkyl and  $m$  is  $2$ .

53. The compound of claim 52, wherein Z is  $Y_3C-O-$  and the groups Y are identical and

represent phenyl substituted with one C<sub>1-3</sub> alkoxy group.

54. The compound of claim 49, wherein Z is Y<sub>2</sub>C=CH- and the groups Y are identical and selected from phenyl, 4-methoxyphenyl and 3-methyl-2-thienyl.

55. The compound of claim 49, wherein

R<sup>1</sup> to R<sup>7</sup> are each H;

A<sup>1</sup> represents (-CR<sup>8</sup>R<sup>9</sup>-)<sub>n</sub>, R<sup>8</sup> and R<sup>9</sup> are independently selected from H and methyl, and

n = 1 or 2;

X is COOM and M is selected from H and Na;

A<sup>2</sup> is (-CR<sup>10</sup>R<sup>11</sup>-)<sub>m</sub>, where R<sup>10</sup> and R<sup>11</sup> are independently selected from H and methyl and m is 2; and

Z is Y<sub>3</sub>C-O- and the groups Y are identical and selected from phenyl groups para-substituted with a C<sub>1-2</sub> alkoxy group.

56. The compound of claim 49, wherein

R<sup>1</sup> to R<sup>7</sup> are each H;

A<sup>1</sup> represents (-CR<sup>8</sup>R<sup>9</sup>-)<sub>n</sub>, R<sup>8</sup> and R<sup>9</sup> are independently selected from H and methyl, and n =

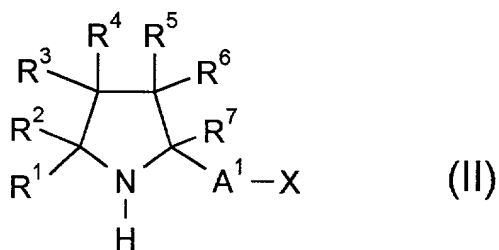
1 or 2;

X is COOM and M is selected from H and Na;

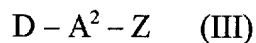
A<sup>2</sup> is (-CR<sup>10</sup>R<sup>11</sup>-)<sub>m</sub>, where R<sup>10</sup> and R<sup>11</sup> are independently selected from H and methyl and m is 2; and

Z is  $Y_2C=CH-$  and the groups Y are identical and selected from phenyl, 4-methoxyphenyl and 3-methyl-2-thienyl.

57. A process for the preparation of a compound of general formula (I) of claim 31, wherein a compound of general formula (II)



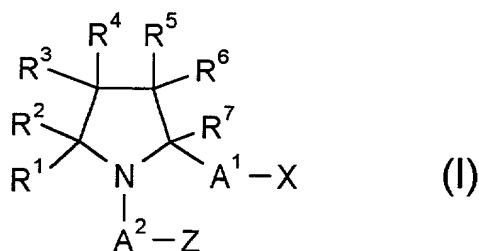
wherein  $R^1$  to  $R^7$ ,  $A^1$  and X are as defined in claim 31 is reacted with a compound of the general formula (III):



wherein  $A^2$  and Z are defined as in claim 31 and D represents a group which can react with the group N-H of the compound of general formula (II) to form HD.

58. The process of claim 57, wherein D is halogen.

59. A pharmaceutical composition comprising at least one of a pharmaceutically acceptable carrier and a pharmaceutically acceptable excipient and at least one compound of general formula (I):



wherein

$R^1$  to  $R^7$  are independently selected from H, optionally substituted  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl, optionally substituted aryl or heteroaryl, OH, halogen, CN,  $OR^{12}$ ,  $SR^{12}$ ,  $COR^{12}$ ,  $COOR^{12}$ ,  $SOR^{12}$ ,  $SO_2R^{12}$ ,  $NR^{13}R^{14}$ ,  $CONR^{13}R^{14}$ ,  $SO_2NR^{13}R^{14}$ , where  $R^{13}$  and  $R^{14}$  are independently selected from H and  $C_{1-3}$  alkyl and  $R^{12}$  represents  $C_{1-6}$  alkyl; two of  $R^1$  to  $R^7$ , together with the atoms connecting them, each may form a 3- to 6-membered ring system, which ring system may contain one or more heteroatoms;  $R^1$  and  $R^2$  and/or  $R^3$  and  $R^4$  and/or  $R^5$  and  $R^6$  may be replaced by an optionally substituted alkylidene group or =O; and two of  $R^1$  to  $R^7$  which are positioned at adjacent carbon atoms may each be replaced by a C-C bond;

$A^1$  is selected from  $(-CR^8R^9-)_n$ , optionally substituted  $C_{3-6}$  cycloalkylene and a combination of these groups,  $R^8$  and  $R^9$  being independently selected from H,  $C_{1-6}$  alkyl, halogen, OH,  $OR^{12}$  and  $NR^{13}R^{14}$  and where for  $n \geq 2$ ,  $R^8$  and  $R^9$  may be different in each group and two groups selected from  $R^8$  and  $R^9$  at adjacent C atoms may be replaced by a C-C bond, and a group -O- or -CO- may be positioned between two adjacent groups  $CR^8R^9$ ; and wherein one of  $R^8$  and  $R^9$  may be combined with one of  $R^1$  to  $R^7$  to form a 5- to 7-membered ring structure; and  $n = 0, 1, 2, 3$  or  $4$ ;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and pharmaceutically acceptable cations;

$A^2$  is  $(-CR^{10}R^{11}-)_m$ , where  $R^{10}$  and  $R^{11}$  are independently selected from H,  $C_{1-2}$  alkyl and halogen; where for  $m \geq 2$  the groups  $R^{10}$  and  $R^{11}$  may be different in each group, a group -O- or -S- may be positioned between two adjacent groups  $-CR^{10}R^{11}-$ , and two groups selected from  $R^{10}$  and  $R^{11}$  at adjacent C atoms may be replaced by a C-C bond; and wherein one of  $R^{10}$  and  $R^{11}$  may be combined with one of  $R^1$  to  $R^9$  to form a 5- to 7-membered ring structure; and m is 1, 2, 3, or 4;

Z is selected from  $Y_3C-O-$ ,  $Y_2C=CR^{15}-$  and  $Y_2C=N-O-$ , where  $R^{15}$  is selected from H,  $C_{1-3}$  alkyl or halogen and the groups Y are independently selected from optionally substituted  $C_{6-12}$  aryl and optionally substituted  $C_{2-5}$  heteroaryl having up to three heteroatoms independently selected from N, O and S, and the groups Y may be linked by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from -O-, -S-, -NH-, -O-, -CH=CH-, -CH=N-, -CH<sub>2</sub>- and -CH<sub>2</sub>CH<sub>2</sub>-;

60. The pharmaceutical composition of claim 59, wherein

$R^1$  to  $R^7$  are independently selected from H,  $C_{1-3}$  alkyl and phenyl;

$A^1$  represents  $(-CR^8R^9-)_n$ ,  $R^8$  and  $R^9$  are independently selected from H and  $C_{1-3}$  alkyl, and  $n = 1$  or  $2$ ;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and Na;

$A^2$  is  $(-CR^{10}R^{11}-)_m$ , where  $R^{10}$  and  $R^{11}$  are independently selected from H and  $C_{1-2}$  alkyl and m is 2 or 3; and


Z is selected from  $Y_3C-O-$  and  $Y_2C=CR^{15}-$ ,  $R^{15}$  is selected from H and methyl and the groups Y are identical and selected from optionally substituted  $C_{6-12}$  aryl and optionally substituted  $C_{2-5}$

heteroaryl having up to three heteroatoms independently selected from N, O and S.

61. A method of treating a disease which can be one of ameliorated and cured by amplification of GABAergic neurotransmission, the method comprising administering to a patient in need of such treatment a compound of claim 31 in an amount sufficient to ameliorate or cure the disease.---

Should there be any questions, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,  
K. WANNER et al.

  
Neil F. Greenblum  
Reg. No. 28,394

*Rec'd.*  
3/1/02

June 4, 2001  
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09/763617

P20670.A01

JC03 Rec'd PCT/PTO 02 MAR 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant :K. WANNER et al.

Serial No. : Not Yet Assigned

PCT Branch

Filed :September 3, 1999

PCT/EP99/06486

For :GABA UPTAKE INHIBITORS HAVING A PYRROLIDINE STRUCTURE

FIRST PRELIMINARY AMENDMENT

Commissioner of Patents and Trademarks  
Washington, D.C. 20231

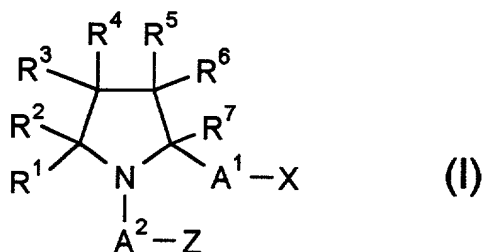
Sir:

Prior to the calculation of the filing fee or examination of the above-identified patent application, the Examiner is respectfully requested to amend the claims as follows:

IN THE CLAIMS

Please cancel claims 1-15 without prejudice or disclaimer. Please enter the following claims 16-30 for consideration by the Examiner:

---16. Compound of general formula (I)



wherein

$R^1$  to  $R^7$  are independently selected from H, optionally substituted  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl, optionally substituted aryl or heteroaryl, OH, halogen, CN,  $OR^{12}$ ,  $SR^{12}$ ,  $COR^{12}$ ,  $COOR^{12}$ ,  $SOR^{12}$ ,  $SO_2R^{12}$ ,  $NR^{13}R^{14}$ ,  $CONR^{13}R^{14}$ ,  $SO_2NR^{13}R^{14}$ , where  $R^{13}$  and  $R^{14}$  are independently selected from H and  $C_{1-3}$  alkyl and  $R^{12}$  represents  $C_{1-6}$  alkyl; two of  $R^1$  to  $R^7$  each may be combined to form a 3- to 6-membered ring system, which ring system may contain one or more heteroatoms;  $R^1$  and  $R^2$  and/or  $R^3$  and  $R^4$  and/or  $R^5$  and  $R^6$  may be replaced by an optionally substituted alkylidene group or =O; and two of  $R^1$  to  $R^7$  which are positioned at adjacent carbon atoms may each be replaced by a C-C bond;

$A^1$  represents  $(-CR^8R^9)_n$ , optionally substituted  $C_{3-6}$  cycloalkylene or a combination of these groups,  $R^8$  and  $R^9$  being independently selected from H,  $C_{1-6}$  alkyl, halogen, OH,  $OR^{12}$  and  $NR^{13}R^{14}$  and where for  $n = 2$   $R^8$  and  $R^9$  may be different in each group and two groups selected from  $R^8$  and  $R^9$  at adjacent C atoms may be replaced by a C-C bond, and a group -O- or -CO- may be positioned between two adjacent groups  $CR^8R^9$ ; and wherein one of  $R^8$  and  $R^9$  may be combined with one of



$R^1$  to  $R^7$  to form a 5- to 7-membered ring structure; and  $n = 0, 1, 2, 3$  or  $4$ ;

X is COOM or a group which can be converted into COOM under physiological conditions, M representing H or a pharmaceutically acceptable cation;

$A^2$  is  $(-CR^{10}R^{11})_m$ , where  $R^{10}$  and  $R^{11}$  are independently selected from H,  $C_{1-2}$  alkyl and halogen; where for  $m = 2$  the groups  $R^{10}$  and  $R^{11}$  may be different in each group, a group -O- or -S- may be positioned between two adjacent groups, and two groups selected from  $R^{10}$  and  $R^{11}$  at adjacent C atoms may be replaced by a C-C bond; and wherein one of  $R^{10}$  and  $R^{11}$  may be combined with one of  $R^1$  to  $R^9$  to form a 5- to 7-membered ring structure; and  $m$  is 1, 2, 3, or 4;

Z is selected from  $Y_3CO$ ,  $Y_2C=CR^{15}$  and  $Y_2C=N-O$ , where  $R^{15}$  is H,  $C_{1-3}$  alkyl or halogen and the groups Y independently are optionally substituted  $C_{6-12}$  aryl or optionally substituted  $C_{2-5}$  heteroaryl having up to three heteroatoms selected from N, O and S, and the groups Y may be linked by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from -O-, -S-, -NH-, -O-, -CH=CH-, -CH=N-, -CH<sub>2</sub>- and -CH<sub>2</sub>CH<sub>2</sub>-;

as well as the individual stereoisomers of these compounds.

17. Compound according to claim 16, wherein  $R^7$  is hydrogen and  $R^1$  to  $R^6$  are independently selected from optionally substituted  $C_{1-3}$  alkyl, halogen, OH, CN, optionally substituted phenyl and optionally substituted heteroaryl having 5 to 10 ring members and one or two heteroatoms selected

from O, N and S, and in particular from hydrogen, C<sub>1-3</sub> alkyl and phenyl.

18. Compound according to claims 16, wherein all of R<sup>1</sup> to R<sup>7</sup> represent hydrogen.

19. Compound according to claim 16, wherein A<sup>1</sup> is (-CR<sup>8</sup>R<sup>9</sup>-)<sub>n</sub>, R<sup>8</sup> and R<sup>9</sup> being independently selected from H and C<sub>1-3</sub> alkyl and being particularly hydrogen and n having a value of 0, 1 or 2, in particular of 1 or 2.

20. Compound according to claim 16, wherein X is COOM, with M = H, Na, K, NH<sub>4</sub>, Ca<sub>0.5</sub> or Mg<sub>0.5</sub>, and preferably H or Na.

21. Compound according to claim 16, wherein R<sup>10</sup> and R<sup>11</sup> are independently selected from H and C<sub>1-2</sub> alkyl, and preferably are both H, and m is 2 or 3, in particular 2.

22. Compound according to claim 16, wherein Z is Y<sub>2</sub>CO and the groups Y, which preferably are the same, are phenyl which optionally is substituted with one or two substituents, the substituents being selected from C<sub>1-3</sub> alkoxy, C<sub>1-3</sub> alkyl, halogen, OH, NO<sub>2</sub>, CN and NR<sup>13</sup>R<sup>14</sup> and R<sup>13</sup> and R<sup>14</sup> are defined as in claim 1.

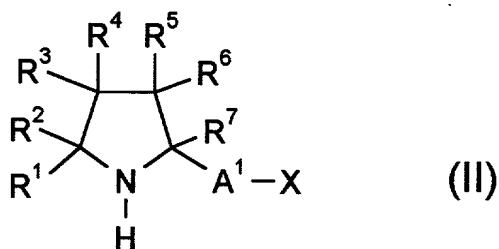
23. Compound according to claim 22, wherein the phenyl radicals are mono- or disubstituted and the substituents are preferably selected from C<sub>1-2</sub> alkoxy, in particular methoxy, and C<sub>1-2</sub> alkyl, in particular methyl.

24. Compound according to claim 16, wherein Z is  $Y_2C=CR^{15}$  or  $Y_2C=N-O$ , the groups Y being preferably the same and representing optionally substituted phenyl or optionally substituted heteroaryl having 5 or 6 ring members and one or two heteroatoms selected from O, N and S and  $R^{15}$  is H or  $CH_3$ , preferably H.

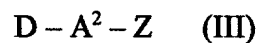
25. Compound according to claim 24, wherein the radicals Y carry 0, 1 or 2 substituents, the substituents being selected from  $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy, halogen, OH,  $NO_2$ , CN and  $NR^{13}R^{14}$ , as defined in claim 1.

26. Compounds according to claim 16, wherein the substituents Y are the same and are selected from phenyl, 4-methoxyphenyl and 3-methyl-2-thienyl.

27. Process for the preparation of a compound of general formula (I), according to claim 16, wherein a compound of general formula (II)



wherein  $R^1$  to  $R^7$ ,  $A^1$  and  $X$  are as defined in claim 16 is reacted with a compound of the general formula (III):



wherein  $A^2$  and  $Z$  are defined as in claim 16 and  $D$  represents a group which can react with the group N-H of the compound of general formula (II) to form HD, in particular halogen.

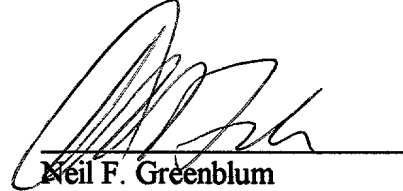
28. Pharmaceutical composition, comprising at least one pharmaceutically acceptable carrier or excipient and at least one compound of general formula (I) as defined in claim 16.

29. Compound according to claim 16 for use in a method for the treatment of the human or animal body.

30. Use of the compound according to claim 16 for the manufacture of a medicament for the treatment of diseases which can be ameliorated or cured by an amplification of the GABAergic neurotransmission.---

Should there be any questions, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,  
K. WANNER et al.



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GABA Uptake Inhibitors Having A Pyrrolidine Structure

**Description**

The present invention relates to GABA uptake inhibitors having a pyrrolidine structure. The present invention further relates to pharmaceutical compositions containing such compounds, as well as to the use of these compounds for the treatment of disorders of the central nervous system (CNS) in which GABA uptake inhibitors play a role, e.g., epilepsy and Chorea Huntington.

With about 50 million affected patients, epilepsy is still one of the most common brain disorders. Due to the large variety of seizure forms and a still present lack of aetiological understanding, to date therapy approaches are limited to controlling the symptoms, e.g., suppressing epileptic fits.

The rudiments of modern therapy go back to the middle of the last century, where bromides were proposed for the treatment of epileptics. It was only in 1912 when the anticonvulsive activity of phenobarbital was discovered. Soon thereafter the first hydantoin derivative was used as antiepileptic. Like phenobarbital, phenytoin, a hydantoin derivative which was introduced in 1938, is still on the market today and is used with Grand Mal, a primarily generalized seizure form of epilepsy.

In the late 60'ies the list of antiepileptics was extended by the group of the benzodiazepines, examples whereof are diazepam and clonazepam.

The mechanisms of action of the individual representatives vary strongly. It did turn out, however, that the  $\gamma$ -aminobutyric acid (GABA)-mediated inhibition of excitation transmission is a primary starting point.

After almost one century of a purely empirical development of the antiepileptics, methods for the purposive development of antiepileptics arose only in the last two decades when people started to understand the molecularbiological context.

In the 50'ies the discovery of GABA in the brains of mammals was reported, without understanding, however, the function thereof. At that time it was presumed for the first time that GABA possibly functions as an inhibitor in the CNS. In 1971 it was finally possible to detect the presence of GABA receptors. Today one distinguishes between GABA<sub>A</sub> and GABA<sub>B</sub> receptors, and in the meantime it has been found out that the GABA<sub>A</sub> receptor is a ion channel protein which is composed of various subunits.

Already in 1968 a high affinity GABA transport system was discovered in rat cortex cuts, which system provides for the uptake of neurotransmitters released into the synaptic gap and, thus, for the termination of the neurotransmitter signal. The isolation of such a GABA transport protein was first accomplished in 1978.

According to more recent studies, with a proportion of 0.1 % of the membrane proteins, GABA uptake proteins occur relatively frequently in the nervous system. In the meantime four different representatives of neurotransmitter transport proteins could be detected by cloning and heterologous expression. The first representative of that family, the cloning whereof was accomplished starting from cDNA, was named GAT-1. This protein also is the first neurotransmitter transporter that was successfully cloned and expressed. Only shortly thereafter human GAT-1 was cloned.

1992 two further transport proteins were identified and named GAT-2 and GAT-3, respectively. Of these, the GAT-3 protein could also be cloned and expressed. GAT-2 probably plays only a minor role in the brains of mammals. It can only be found in the pia mater, as well as in the liver.

The forth representative of the family of uptake proteins is a common transport system for betaine and GABA which occurs, inter alia, in the kidney, and was named BGT-1.

Already in 1975, in studies with nipecotic acid, guvacine and arecaidine, active agents from the betel nut (*Areca catechu*), the inhibiting effect of nipecotic acid and guvacine on the uptake of GABA was discovered. With the knowledge about the relationships in the GABAergic neurotransmission, new strategies in the therapy of epilepsy arose. For example, it is thus possible to enhance the neuronal GABA transmission by direct GABA mimetics. GABA itself is not suitable for this since it cannot pass the blood-brain barrier. A problem of said direct GABA mimetics is that a tolerance may develop thereby. Moreover, they amplify the GABAergic neurotransmission in an unspecific manner in the GABAergic synapses in general, and not only where signals arrive. Those mechanisms of action which enhance the GABAergic neurotransmission only when transmitter is released represent a particularly sensible therapy approach. This can be achieved, on the one hand, by inhibiting the degradation of the transmitter and, on the other hand, by inhibiting the uptake thereof. The starting point for the development of corresponding GABA uptake inhibitors were the already mentioned compounds nipecotic acid and guvacine.

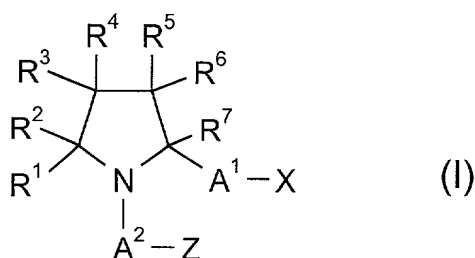
However, like GABA these compounds can pass the blood-brain barrier only with great difficulty or not at all.

Meanwhile some compounds which can pass into the CNS and at the same time show a substantial affinity towards GABA uptake proteins have been described in the literature. However, so far all of these compounds only show a high GAT-1 selectivity, whereas even today there are substantially no compounds which show GAT-3 selectivity.

Thus the problem underlying the present invention in general was the provision of new GABA uptake inhibitors and, in particular, the provision of GABA uptake inhibitors having a high selectivity towards GAT-3 (or at least high selectivity towards GAT-1).

According to the present invention the above problem is solved by compounds of the general formula (I)





wherein

$R^1$  to  $R^7$  are independently selected from H, optionally substituted  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl, optionally substituted aryl or heteroaryl, OH, halogen (particularly F and Cl), CN,  $OR^{12}$ ,  $SR^{12}$ ,  $COR^{12}$ ,  $COOR^{12}$ ,  $SOR^{12}$ ,  $SO_2R^{12}$ ,  $NR^{13}R^{14}$ ,  $CONR^{13}R^{14}$ ,  $SO_2NR^{13}R^{14}$ , where  $R^{13}$  and  $R^{14}$  are independently selected from H and  $C_{1-3}$  alkyl and  $R^{12}$  represents  $C_{1-6}$  alkyl; two of  $R^1$  to  $R^7$  each may be combined to form a 3- to 6-membered ring system, which ring system may contain one or more heteroatoms;  $R^1$  and  $R^2$  and/or  $R^3$  and  $R^4$  and/or  $R^5$  and  $R^6$  may be replaced by an optionally substituted alkylidene group or  $=O$ ; and two of  $R^1$  to  $R^7$  which are positioned at adjacent carbon atoms each may be replaced by a C-C bond;

$A^1$  represents  $(-CR^8R^9)_n$ , optionally substituted  $C_{3-6}$  cycloalkylene or a combination of these groups,  $R^8$  and  $R^9$  being independently selected from H,  $C_{1-6}$  alkyl, halogen, OH,  $OR^{12}$  and  $NR^{13}R^{14}$  and where for  $n \geq 2$   $R^8$  and  $R^9$  may be different in each group and two groups selected from  $R^8$  and  $R^9$  at adjacent C atoms may be replaced by a C-C bond, and a group -O- or -CO- may be positioned between two adjacent groups  $CR^8R^9$ ; and wherein one of  $R^8$  and  $R^9$  may be combined with one of  $R^1$  to  $R^7$  to form a 5- to 7-membered ring structure; and  $n = 0, 1, 2, 3$  or  $4$ ;

X is COOM or a group which can be converted into COOM under physiological conditions, M representing H or a pharmaceutically acceptable cation;

$A^2$  is  $(-CR^{10}R^{11})_m$ , where  $R^{10}$  and  $R^{11}$  are independently selected from H,  $C_{1-2}$  alkyl and halogen; where for  $m \geq 2$  the groups  $R^{10}$  and  $R^{11}$  may be different in each group, a group

-O- or -S- may be positioned between two adjacent groups, and two groups selected from  $R^{10}$  and  $R^{11}$  at adjacent C atoms may be replaced by a C-C bond; and wherein one of  $R^{10}$  and  $R^{11}$  may be combined with one of  $R^1$  to  $R^9$  to form a 5- to 7-membered ring structure; and m is 1, 2, 3, or 4;

Z is selected from  $Y_3CO$ ,  $Y_2C=CR^{15}$  and  $Y_2C=N-O$ , where  $R^{15}$  is H,  $C_{1-3}$  alkyl or halogen and the groups Y independently are optionally substituted  $C_{6-12}$  aryl or optionally substituted  $C_{2-5}$  heteroaryl having up to three heteroatoms selected from N, O and S, and the groups Y may be linked by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from -O-, -S-, -NH-, -O-, -CH=CH-, -CH=N-, -CH<sub>2</sub>- and -CH<sub>2</sub>CH<sub>2</sub>-;

as well as the individual stereoisomers of these compounds.

A further object of the present invention are pharmaceutical compositions containing at least one pharmaceutically acceptable carrier or excipient and at least one compound of general formula (I).

Furthermore, the present invention is directed to the use of the compounds of general formula (I) for the manufacture of a medicament for the treatment of diseases where amplification of the GABAergic neurotransmission is of advantage, in particular epilepsy, Chorea Huntington and related disorders of the CNS. The compounds of the present invention can also successfully be employed as anticonvulsants, sedatives, anxiolytics and antidepressants.

In the following the present invention will be further illustrated with reference to preferred embodiments thereof.

Meanings of the radicals  $R^1$  to  $R^7$ :

The term “optionally substituted C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl and C<sub>2-6</sub> alkynyl” is to denote groups that are unsubstituted or carry (preferably, one or two) substituents selected, in particular, from OH, halogen (particularly F, Cl, Br, and particularly preferred F), CN, NO<sub>2</sub> and OR<sup>12</sup>. However, the substituents may also (and additionally) be (optionally substituted) aryl or heteroaryl radicals (as defined in more detail hereafter). As specific examples of the radicals R<sup>1</sup> to R<sup>7</sup> just discussed there may be mentioned methyl, ethyl, propyl, CF<sub>3</sub>, CH<sub>2</sub>OCH<sub>3</sub>, CH<sub>2</sub>OH, benzyl and phenethyl.

“Optionally substituted aryl or heteroaryl” includes aryl groups having preferably 6 to 12 C atoms and heteroaryl radicals having 5 to 12 ring members, up to three of which may be heteroatoms (in general selected from N, O and S). These aryl or heteroaryl radicals may be unsubstituted or substituted (by preferably one to three substituents). Preferred examples of such substituents are C<sub>1-3</sub> alkyl, C<sub>2-4</sub> alkenyl, OH, halogen (in particular, F, Cl, Br), CN, NO<sub>2</sub>, OR<sup>12</sup> and NR<sup>13</sup>R<sup>14</sup>. As specific examples there may be mentioned in this context phenyl, thienyl, furanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyridinyl, pyranil and corresponding radicals carrying one to three (preferably one) substituent from the group methyl, ethyl, CF<sub>3</sub>, methoxy, ethoxy, F, Cl, CN, NH<sub>2</sub>, dimethylamino and diethylamino.

If R<sup>1</sup> to R<sup>7</sup> represent halogen, said halogen preferably is fluorine or chlorine, particularly preferred fluorine. It is preferred for R<sup>1</sup>, R<sup>2</sup> and R<sup>7</sup> to be different from halogen, OR<sup>12</sup>, SR<sup>12</sup> and NR<sup>13</sup>R<sup>14</sup>, since otherwise there is the possibility of enamine formation.

The radical R<sup>12</sup> preferably is C<sub>1-3</sub> alkyl, in particular methyl and ethyl. R<sup>13</sup> and R<sup>14</sup> are preferably the same and preferably represent methyl and ethyl. However, R<sup>13</sup> and R<sup>14</sup> may also form an alkylene group, resulting in, for example, a pyrrolidinyl or piperidinyl radical.

In a particularly preferred compound of general formula (I), R<sup>1</sup> to R<sup>6</sup> are independently selected from H, optionally substituted C<sub>1-3</sub> alkyl, halogen, OH, CN, optionally substituted phenyl and optionally substituted heteroaryl having five to ten ring members

and one or two heteroatoms selected from O, N and S, and particularly from hydrogen, C<sub>1-3</sub> alkyl and phenyl. R<sup>7</sup> preferably is H. In general it is preferred that not more than two and particularly not more than one of the radicals R<sup>1</sup> to R<sup>7</sup> is different from H. It may be of particular advantage if all of R<sup>1</sup> to R<sup>7</sup> represent hydrogen.

Also, two each of R<sup>1</sup> to R<sup>7</sup> may be combined to form a 3- to 6-membered ring system (preferably, a 5- or 6-membered ring system) which furthermore may contain one or more (preferably, one or two) heteroatoms. Preferably, the heteroatoms are O, N or S. Moreover, R<sup>1</sup> and R<sup>2</sup> and/or R<sup>3</sup> and R<sup>4</sup> and/or R<sup>5</sup> and R<sup>6</sup> may be replaced by an optionally substituted alkylidene group or oxo (=O). It is preferred that, if present at all, only one such alkylidene or oxo group is present on the ring. The substituents which may optionally be present on the alkylidene group (preferably one to three) are preferably those that have been given above as examples of substituents on alkyl, alkenyl and alkynyl radicals R<sup>1</sup> to R<sup>7</sup>. Finally, two of R<sup>1</sup> to R<sup>7</sup>, which are located on adjacent C atoms, each may be replaced by a C-C bond. This results in the presence of double and triple bonds in the ring. Preferred in this context is a double bond between the 3- and 4-position of the pyrrolidine skeleton. A pyrrole structure is also worth mentioning in this context.

If A<sup>1</sup> represents a combination of (-CR<sup>8</sup>R<sup>9</sup>-)<sub>n</sub> and (optionally substituted) C<sub>3-6</sub> cycloalkylene, this is to mean that A<sup>1</sup> may, in particular, be alkylene-cycloalkylene, cycloalkylene-alkylene and alkylene-cycloalkylene-alkylene. It is preferred for A<sup>1</sup> to represent (-CR<sup>8</sup>R<sup>9</sup>-)<sub>n</sub>. Regarding possible meanings of R<sup>8</sup> and R<sup>9</sup> the corresponding explanations in connection with R<sup>1</sup> to R<sup>7</sup> above may be referred to. Particularly preferred meanings of R<sup>8</sup> and R<sup>9</sup> are H and C<sub>1-3</sub> alkyl, in particular methyl. Preferably, only one of R<sup>8</sup> and R<sup>9</sup> is different from H, and it is particularly preferred if both of them are hydrogen. n has values of, in particular, 0, 1 or 2, 1 or 2 being preferred. In the latter case the compounds of the present invention are derivatives of acetic and propionic acid (for R<sup>8</sup>, R<sup>9</sup> = H). These compounds are particularly preferred according to the present invention.

If A<sup>1</sup> is, or includes, optionally substituted C<sub>3-6</sub> cycloalkylene, preferred examples of the cycloalkylene group are cyclopropylene, cyclopentylene and cyclohexylene. Optionally present substituents are preferably selected from C<sub>1-3</sub> alkyl, halogen (e.g., F or Cl) and OH. However, it is preferred for the cycloalkylene radical to not carry any substituents.

If A<sup>1</sup> is, or comprises, (-CR<sup>8</sup>R<sup>9</sup>-)<sub>n</sub>, for n ≥ 2 R<sup>8</sup> and R<sup>9</sup> may be different, both from each other and in each group CR<sup>8</sup>R<sup>9</sup>. Further, in this case two groups selected from R<sup>8</sup> and R<sup>9</sup> on adjacent C atoms each may be replaced by a C-C bond (which may result in a derivative of acrylic acid), and there may be a group -O- or -CO- between adjacent groups CR<sup>8</sup>R<sup>9</sup>, although this is not preferred. Finally, one of R<sup>8</sup> and R<sup>9</sup> (preferably located on a carbon atom which is bonded directly to the ring) may be combined with one of R<sup>1</sup> to R<sup>7</sup> (preferably, R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup>) to form a 5- to 7-membered ring structure. This ring structure may be saturated or unsaturated, and may also contain one or more heteroatoms, preferably selected from O, N and S.

In the general formula (I), X represents COOM or a group that can be converted into COOM under physiological conditions. Among the latter groups there are, for example, ester, nitrile and salts. Preferably, M represents hydrogen and corresponding cations of sodium, potassium, calcium and magnesium, as well as ammonium. H and Na are even more preferred as meanings of M, the most preferred meaning of M being hydrogen.

A<sup>2</sup> in the above general formula (I) is (-CR<sup>10</sup>R<sup>11</sup>-)<sub>m</sub>, with R<sup>10</sup> and R<sup>11</sup> being preferably H, methyl, ethyl and halogen (in particular, F or Cl). Preferably only one of R<sup>10</sup> and R<sup>11</sup> is different from H, and it is particularly preferred for R<sup>10</sup> and R<sup>11</sup> to both represent hydrogen. If R<sup>10</sup> and/or R<sup>11</sup> are halogen, the halogen should not be on the C atom which is adjacent to the N atom (risk of formation of enamine or iminium ion). m preferably has a value of 2 or 3, 2 being particularly preferred. If m ≥ 2 the groups R<sup>10</sup> and R<sup>11</sup> may be different, both from each other and within each group CR<sup>10</sup>R<sup>11</sup>. In particular for m > 2, two adjacent groups CR<sup>10</sup>R<sup>11</sup> may be separated by a group -O- or -S-, and two groups selected from R<sup>10</sup> and R<sup>11</sup> on adjacent C atoms each may be replaced by a C-C bond, resulting in a double (or triple) bond. Also in these cases the C atom adjacent to the N

atom should be free of structural features which (may) result in an enamine or iminium ion structure, respectively. Finally, one of  $R^{10}$  and  $R^{11}$  (preferably located at the C atom bonded to the N atom) may be combined with one of  $R^1$  to  $R^9$  (preferably, with one of  $R^1$ ,  $R^2$ ,  $R^7$ ,  $R^8$  and  $R^9$ ) to form a 5- to 7-membered ring structure, which ring structure may be saturated or unsaturated, and may further have one or more heteroatoms, selected from O, N and S, in addition to the ring nitrogen atom.

If Z stands for  $Y_3CO$ , the groups Y are preferably the same. Furthermore, preferred meanings of Y are optionally substituted phenyl as well as optionally substituted thienyl, furanyl and pyrrolyl. Optionally substituted phenyl is particularly preferred. If substituents are present, their number preferably does not exceed 3, and in particular 2, (only) one substituent being even more preferred. Preferred substituents are selected from  $C_{1-3}$  alkoxy,  $C_{1-3}$  alkyl, halogen, OH,  $NO_2$ , CN and  $NR^{13}R^{14}$ . Specific examples of such substituents are methoxy, ethoxy, methyl, ethyl, F, Cl,  $NH_2$ , dimethylamino and diethylamino. A particularly preferred substituent is  $C_{1-3}$  alkoxy, in particular methoxy. In the case of a phenyl ring this group is preferably in the 2- and/or 4-position, even more preferred in the 4-position.

If Z represents  $Y_2C=CR^{15}$ , the two groups Y are preferably the same as well. Furthermore, preferred meanings for Y in this case are optionally substituted phenyl or optionally substituted heteroaryl having 5 or 6 ring members and one or two heteroatoms selected from O, N and S. Regarding the optionally present substituents, the above comments with respect to the groups Y may be referred to. If Y is phenyl, the phenyl ring is preferably free of substituents. If Y represents heteroaryl, Y preferably is optionally substituted thienyl, particularly 3-methyl-2-thienyl.

$R^{15}$  preferably is H or methyl, even more preferred H.

If Z is  $Y_2C=N-O$ , the two groups Y preferably are also identical. With respect to the preferred meanings of Y the above comments regarding the preferred groups Y for the other meanings of Z may be referred to.

In particularly preferred embodiments of compounds of general formula (I) according to the present invention the various groups have the following meanings, in particular:

$R^1$  to  $R^7$ : hydrogen;

$A^1$ :  $-\text{CH}_2-$  or  $-\text{CH}_2\text{CH}_2-$ , as well as  $-\text{CH}=\text{CH}-$ ;

X:  $\text{COOH}$ ;

$A^2$ :  $-\text{CH}_2\text{CH}_2-$ ;

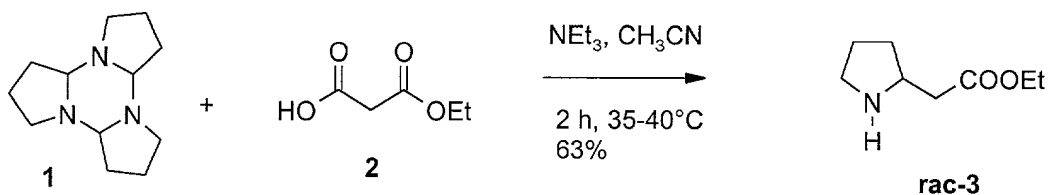
Z:  $(\text{C}_6\text{H}_5)_2\text{C}=\text{CH}-$ ,  $(3\text{-methyl-2-thienyl})_2\text{C}=\text{CH}-$  and  $(4\text{-CH}_3\text{O-C}_6\text{H}_4)_3\text{CO}-$ .

The present invention also includes the individual isomers (enantiomers, diastereomers, optionally cis/trans-isomers) of the compounds of general formula (I) of the present invention. In this context it is to be pointed out that irrespective of the meanings of the various radicals in the general formula, the carbon atom carrying  $R^7$  and  $A^1\text{-X}$  is a chiral center, so that the compounds of the present invention are present as at least enantiomers. The present invention encompasses both the individual enantiomers and the racemates of these compounds.

The compounds of the present invention show a high selectivity towards GAT-3 and/or GAT-1 which is noteworthy; accordingly, they can be used for the treatment of conditions wherein these transport proteins play a role. Epilepsy and Chorea Huntington may particularly be mentioned in this context.

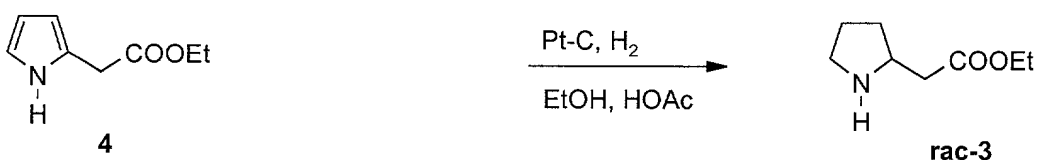
The compounds according to the present invention and the precursors thereof can be synthesized according to conventional processes described in the literature, or in analogy to such processes. In the following some of these processes will be briefly discussed. Individual isomers (enantiomers) may be prepared, in addition to a usual separation (e.g., by resolution of a racemate), also by processes which use chiral auxiliaries in the preparation. Examples of such processes will also be briefly outlined in the following.

## Reaction Scheme 1

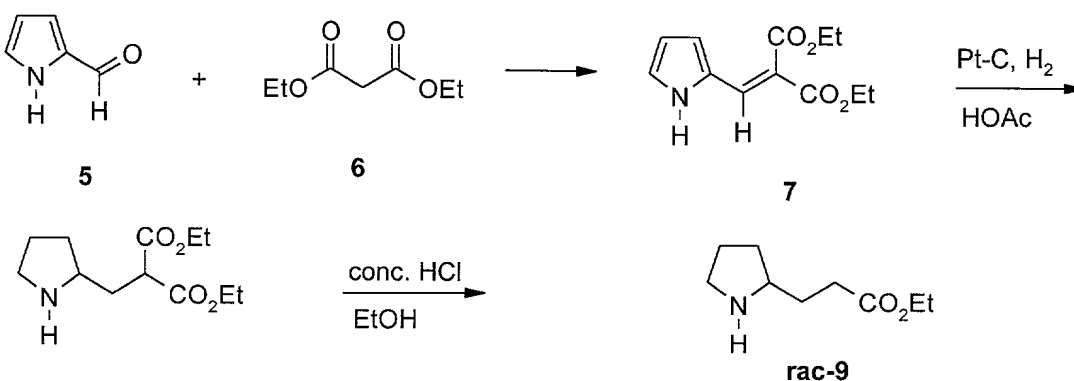


The synthesis of **rac-3** is carried out by reacting **1** with malonic acid monoethyl ester (**2**) according to the procedure of Fukawa et al., *Chem. Letters*, **1982**, 231-232.

Compound **rac-3** is furthermore available by catalytic hydrogenation of **4** with Pt-C as catalyst according to the following procedure: Clemo, Melrose, *J. Chem. Soc.*, **1942**, 424.



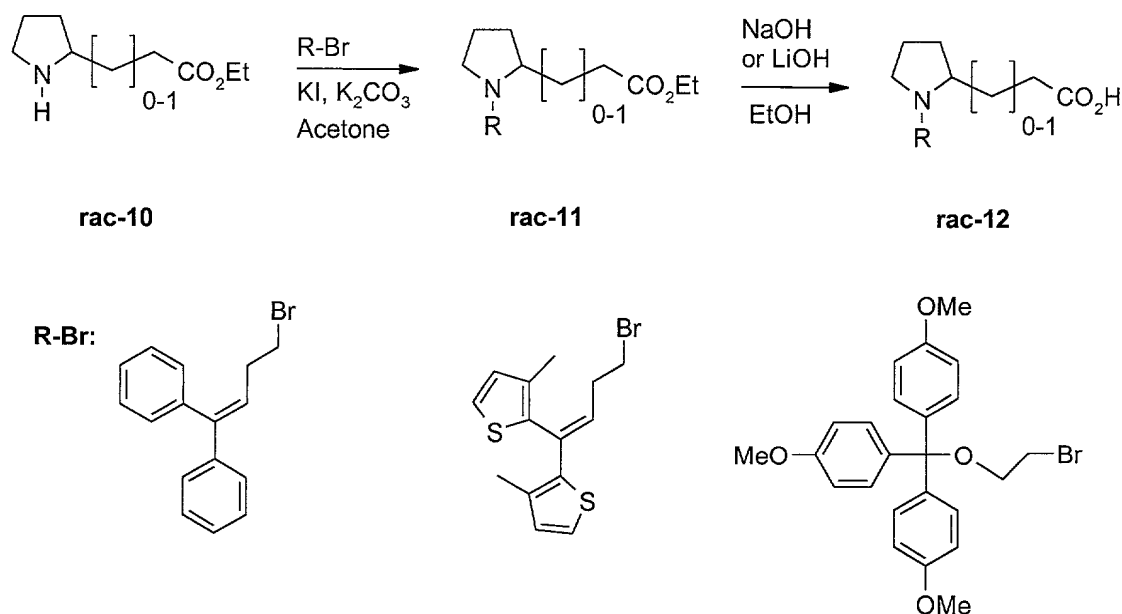
## Reaction Scheme 2





Compound **rac-9** may be synthesized starting from pyrrole-2-carbaldehyde **5** according to the three-step process depicted in Reaction Scheme 2. Condensation product **7** is obtained by reacting **5** with **6** according to the procedure of Ch. Robinson, L. J. Wiseman, J. Leonhard, C. D. Slater, *Tetrahedron*, **1989**, 45, 4103-4112. Subsequent catalytic hydrogenation, ester hydrolysis and decarboxylation according to the procedure of Clemons et al., *J. Chem. Soc.*, **1950**, 1140 results in **rac-9**.

### Reaction Scheme 3



In analogy to known processes, the N-substituted amino acids **rac-12** may be synthesized starting from the amino acids **rac-10** by alkylation with a suitable electrophile and subsequent ester hydrolysis. K. E. Andersen et al., *J. Med. Chem.* **1993**, 36, 1716-1725. T. G. M. Dhar et al., *J. Med. Chem.* **1994**, 37, 2334-2342.

### Preparation of Compounds in Enantiomerically Pure Form

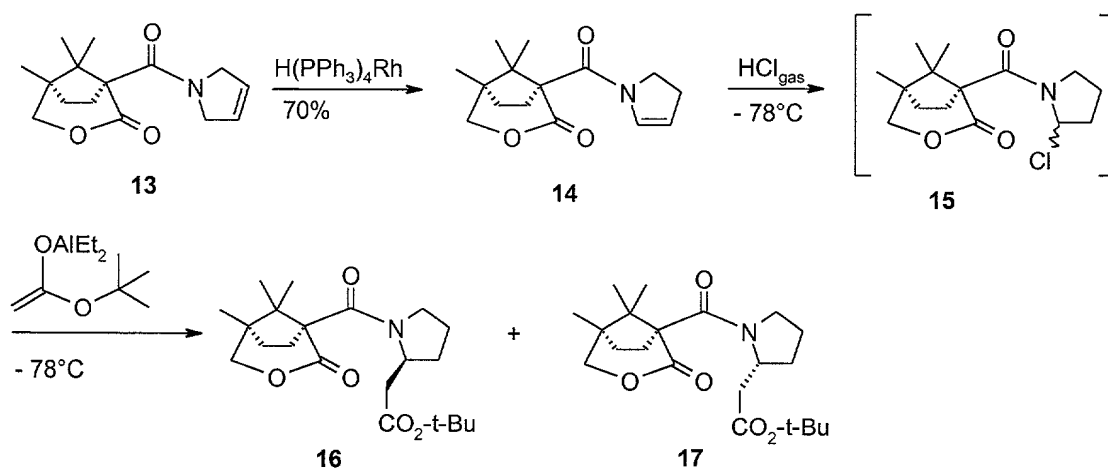
A) For the preparation of the compounds in enantiomerically pure form, for example, the racemates of the amino acid esters **rac-11** may be separated into their enantiomers according to known methods by using enantiomerically pure chiral acids. Hydrolysis of

the enantiomerically pure esters **11** thus obtained according to the already described methods results in the enantiomerically pure amino acids **12**.

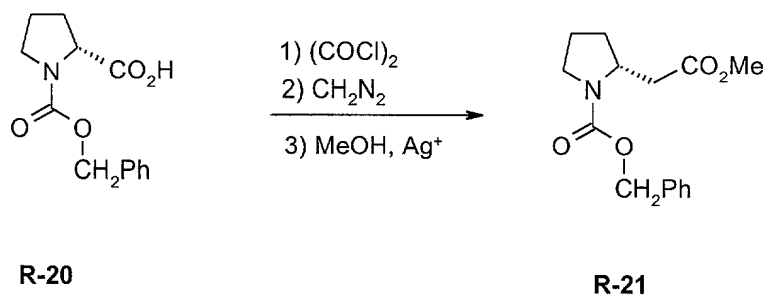
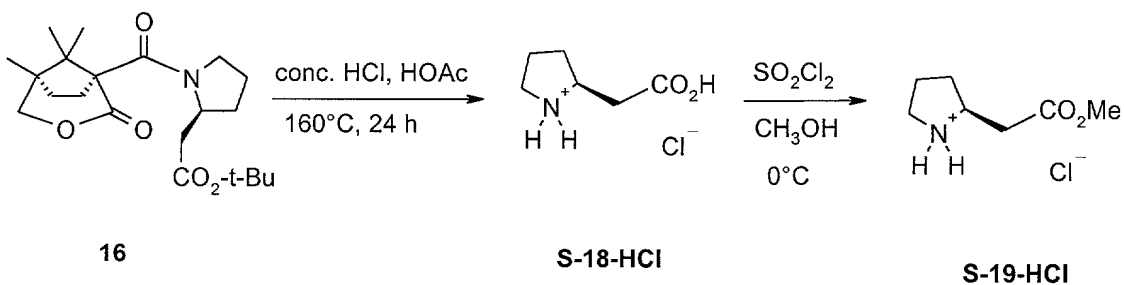
B) Compounds according to the present invention may, additionally, be prepared in enantiomerically pure form according to special processes. The reactions of the following Reaction Schemes **4** to **8** will be explained in the working examples below.

### Basic Skeleton of Pyrrolidine-2-acetic acid

#### Reaction Scheme 4

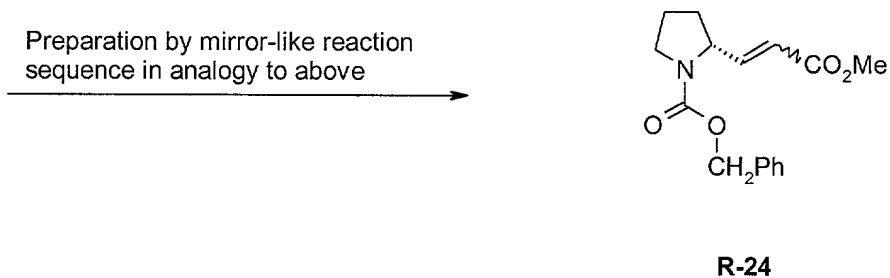
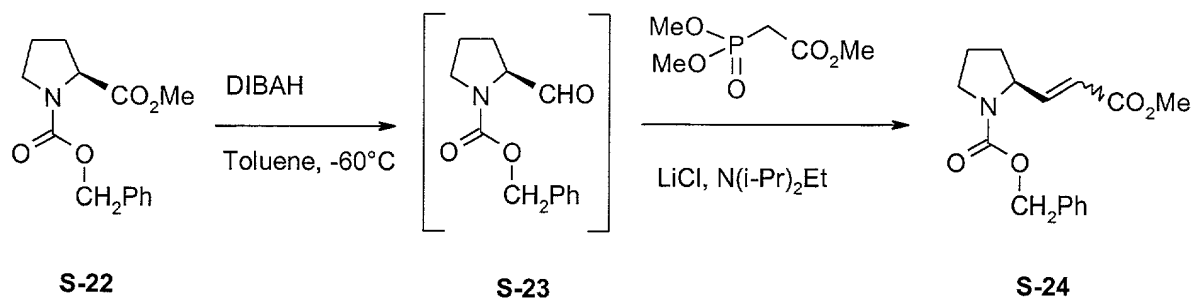


## Reaction Scheme 5

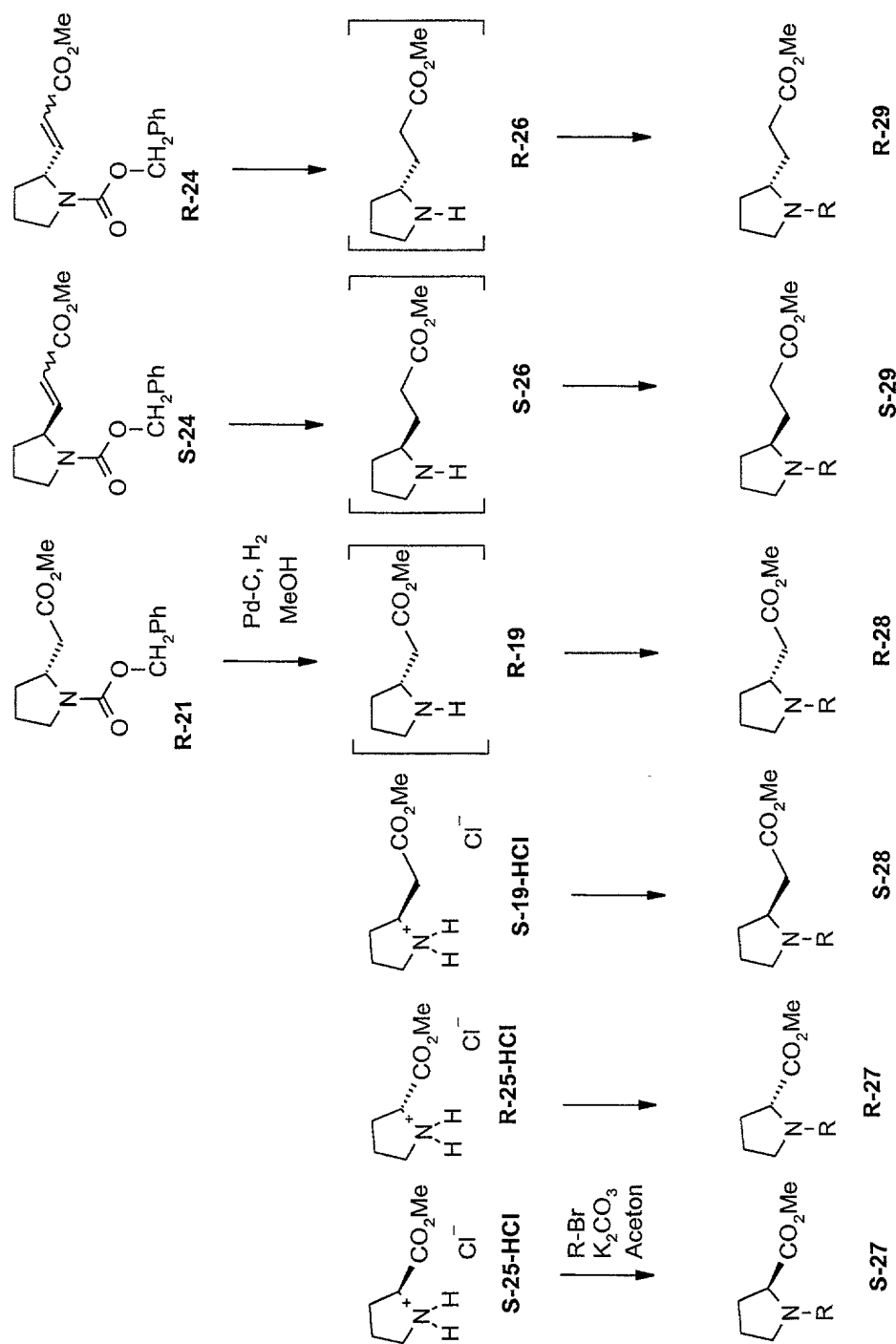


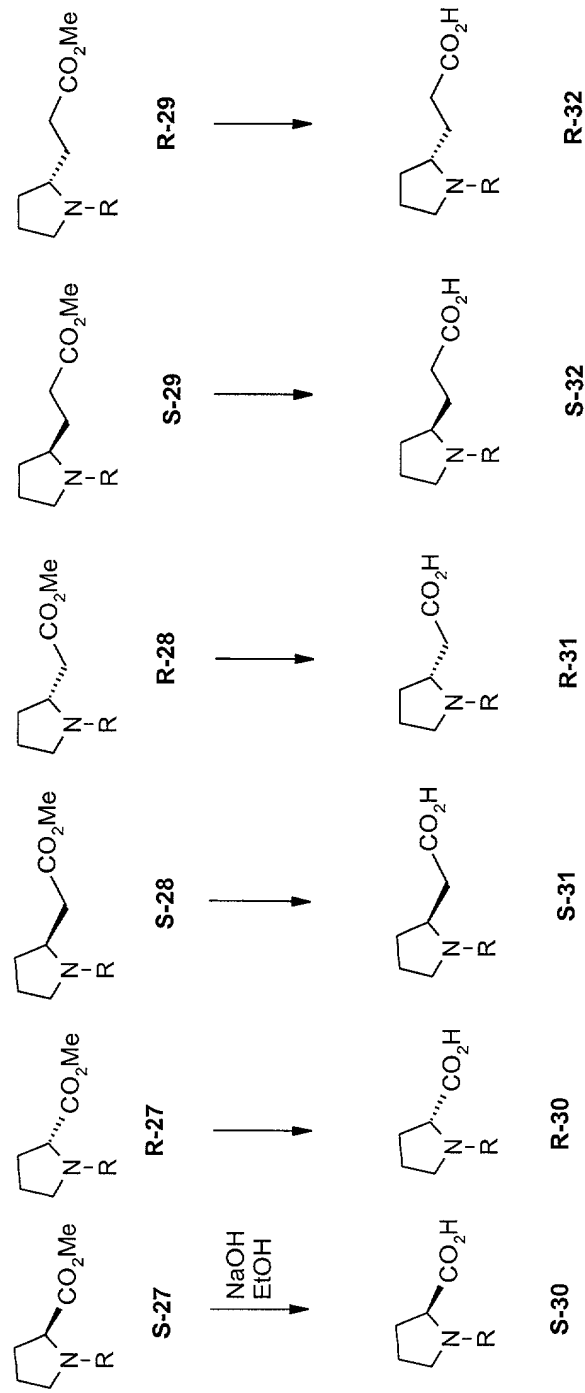
## Basic Skeleton of Pyrrolidin-2-ylpropanoic Acid

## Reaction Scheme 6



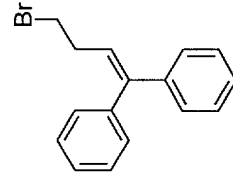
# Reaction Scheme 7



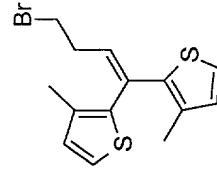


R-Br:

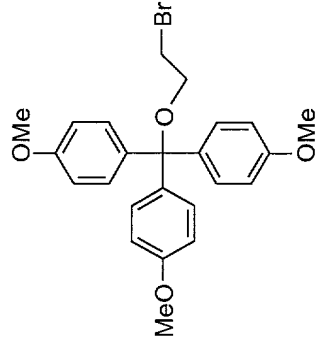
a



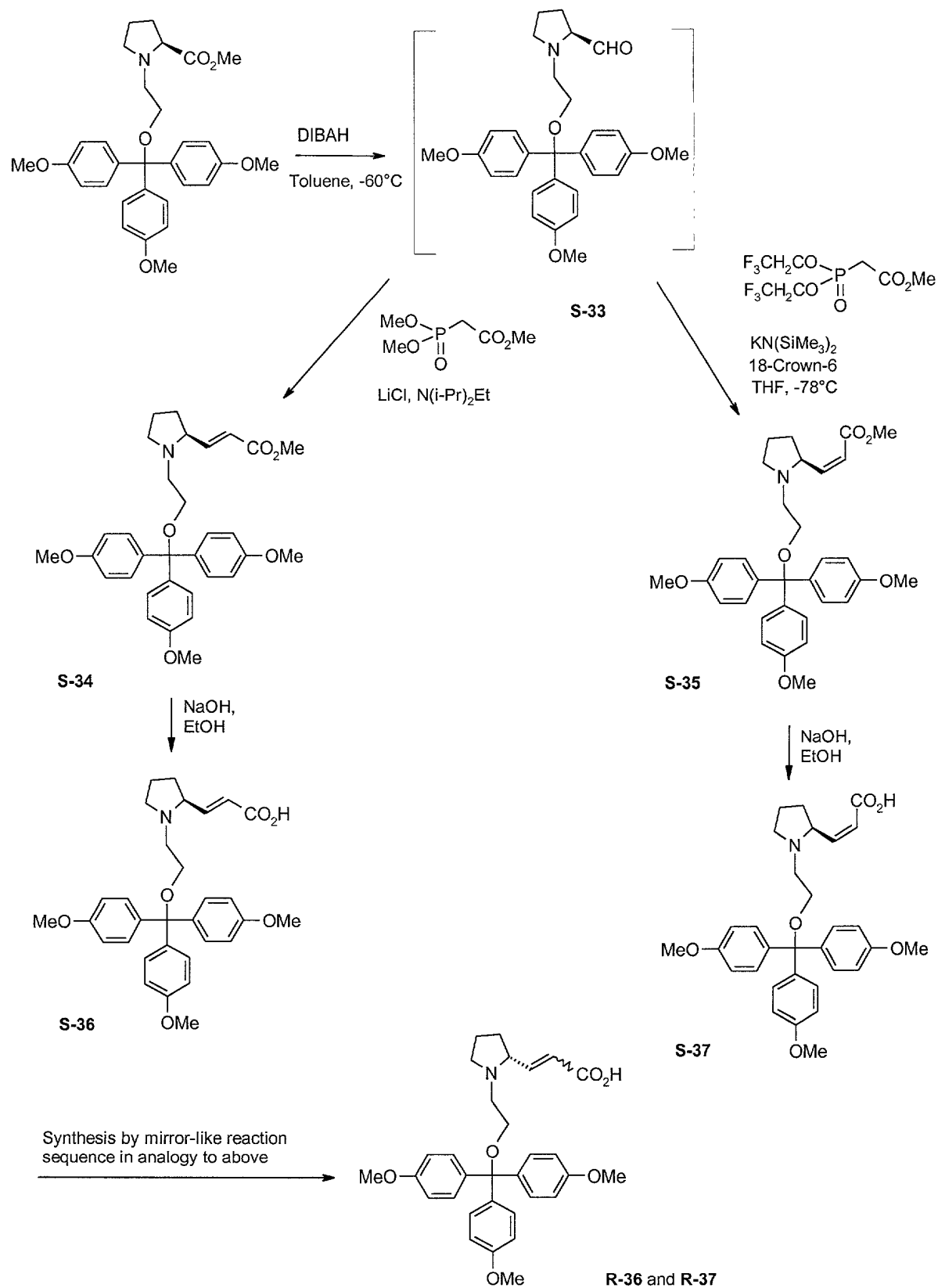
b



c



# Reaction Scheme 8



## Examples

### General details of chemical studies

Melting Points: Melting point apparatus according to Dr. Tottoli (Messrs. Büchi, No. 512). The melting points were not corrected.

Optical Rotations: Polarimeter 241 MC (Messrs. Perkin Elmer).

IR Spectra: FT-IR Spectrometer 1600 and Paragon 1000 (Messrs. Perkin Elmer). The spectra were recorded with a KBr pellet or as film between NaCl plates, respectively.

NMR Spectra: JNMR-GX 400 (Messrs. Jeol, 400 MHz), TMS as internal standard. Coupling constants were given with an accuracy of 0.5 Hz. The post-processing of the spectra was conducted with NUTS, 2D version 4.35, Acorn NMR, 1994.

Mass Spectra: Mass Spectrometer 5989 A with 59980 B Particle Beam LC/MS Interface (Messrs. Hewlett Packard).

Thin Layer Chromatography: DC plates Kieselgel 60 F-254 (Messrs. Merck). Detection was carried out in the UV range (254 nm) or by using a cerium(IV) ammonium molybdate immersion reagent (5 %  $(\text{NH}_4)_x\text{Mo}_7\text{O}_{24}$  and 0.2 %  $\text{Ce}(\text{SO}_4)_2$ , dissolved in 5 % aqueous  $\text{H}_2\text{SO}_4$ ). Detection was carried out by subsequent heating.

Column Chromatography (CC): Flash-Chromatography <sup>[113]</sup> on Kieselgel 60 (particle size 0.040 - 0.063 mm, Messrs. Merck).

Analytical HPLC: Chromatography pumps L-6200 Intelligent-Pump and L-6000 (Messrs. Merck-Hitachi), UV-VIS Detectors L-4000 and L-7400 (242 and 254 nm, respectively, Messrs. Merck-Hitachi), integrators D-7500 and D-2500 (Messrs. Merck-Hitachi), columns: cartridge system LiChroCart<sup>®</sup> (Messrs. Merck):

A) LiChrospher<sup>®</sup> Si 60 (5  $\mu\text{m}$ , 250  $\times$  4 mm with precolumn 4  $\times$  4 mm)

B) LiChrosorb<sup>®</sup> Si 60 (5  $\mu\text{m}$ , 250  $\times$  4 mm with precolumn 4  $\times$  4 mm).

Preparative HPLC: Chromatography pump L-6000 (Messrs. Merck-Hitachi), UV-VIS detector L-4000 (242 and 254 nm, respectively, Messrs. Merck-Hitachi), integrator D-2000 (Messrs. Merck-Hitachi),

Column: Hibar Fertigsäule RT (Messrs. Merck) LiChrosorb<sup>®</sup> Si 60 (7  $\mu\text{m}$ , 250  $\times$  25 mm).

Reagents and solvents: All reagents were of commercial grade. Dried and distilled solvents were used for the reactions. For chromatography, distilled solvents were used which were additionally degassed for HPLC.

Reaction Conditions: If not indicated otherwise, the reactions were carried out in previously heated glass apparatus under N<sub>2</sub> atmosphere.

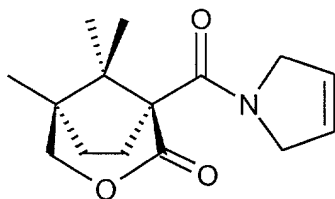
The following abbreviations were used in the description of the experiments:

DBU	1,8-Diazabicyclo[5.4.0.]un-7-decene
DIBALH	Diisobutyl aluminiumhydride
DIPEA	Diisopropyl ethylamine
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
Ether	Diethyl ether
THF	Tetrahydrofuran
TMEDA	N,N,N',N'-Tetramethylethylene diamine
i. vac.	in vacuo



## Preparation Example 1

### (1*S*,5*R*)-1-(2,5-Dihydropyrrol-1-ylcarbonyl)-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (13)

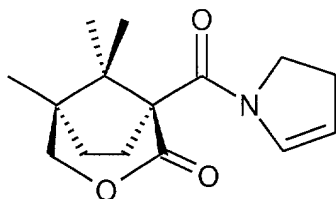


13

3.79 g (14.4 mmol) of (1*S*,5*R*)-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one-1-carboxylic acid was suspended in 60 ml of CH<sub>2</sub>Cl<sub>2</sub>, cooled to 0 °C, and 1.78 g (14.5 mmol) of oxalyl chloride was added thereto. Subsequently DMF (10 drops) was added under strong stirring and the reaction mixture was slowly heated to room temperature. After the evolution of gas had ceased, the flask was purged with a nitrogen stream for one hour to remove HCl. Upon cooling the solution to 0 °C, 3.54 g (2.5 eq.) of triethylamine as well as 1 g (14.4 mmol) of 3-pyrroline were added. Thereafter the reaction mixture was brought to room temperature and stirred for 12 h. Subsequently the reaction mixture was diluted with 30 ml of CH<sub>2</sub>Cl<sub>2</sub>, washed several times with 0.5 N HCl, and the organic phase was dried with MgSO<sub>4</sub> and concentrated. Purification of the residue by column chromatography (petrol ether/ethyl acetate = 7/3) and recrystallization from petrol ether/ethyl acetate (7/3) afforded 3.254 g (86%) of colorless crystals; m.p.: 108 °C.  $[\alpha]_D^{20} = +97.9$  (c = 0.65, CHCl<sub>3</sub>). – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 0 °C): δ = 0.91 (s, 3 H, CH<sub>3</sub>), 1.09 (s, 3 H, CH<sub>3</sub>), 1.38 (s, 3 H, CH<sub>3</sub>), 1.86-1.97 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>), 2.27 (dt, *J* = 11.0/5.1 Hz, 1 H, CH<sub>2</sub>CH<sub>2</sub>), 2.43 (ddd, *J* = 13.9/11.0/5.9 Hz, 1 H, CH<sub>2</sub>CH<sub>2</sub>), 3.94 (d, *J* = 11.3 Hz, 1 H, CH<sub>2</sub>O), 4.15 (dd, *J* = 11.3/2.2 Hz, 1 H, CH<sub>2</sub>O), 4.12-4.18 (m, 1 H, NCH<sub>2</sub>), 4.23 (ddd, *J* = 13.9/4.4/2.2 Hz, 1 H, NCH<sub>2</sub>), 4.39 (ddd, *J* = 13.9/5.1/2.2 Hz, 1 H, NCH<sub>2</sub>), 4.56 (ddd, *J* = 16.9/5.1/2.2 Hz, 1 H, NCH<sub>2</sub>), 5.75 (ddd, *J* = 6.6/4.4/2.2 Hz, 1 H, HC=), 5.85 (ddd, *J* = 6.6/4.4/2.2 Hz, 1 H, HC=).

## Preparation Example 2

### (1*S*,5*R*)-1-(2,3-Dihydropyrrol-1-ylcarbonyl)-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (14)



14

A mixture of 1.0 g of 13 (3.8 mmol) and 15 mg of hydridotetrakis(triphenylphosphine)-rhodium dissolved in 4 ml of abs. xylene was stirred for 44 h at 140 °C in a sealed pressure tube. Subsequently the reaction mixture was filtered, concentrated, purified by column chromatography (petrol ether/ethyl acetate /ethyldimethylamine = 80/20/1), and recrystallized from cyclohexane. Yield: 700 mg (70%); colorless crystals; m.p.: 105 °C.  $[\alpha]_D^{20} = +46.3$  (c = 0.68, CHCl<sub>3</sub>). – <sup>1</sup>H NMR ([D<sub>5</sub>]nitrobenzene, 130 °C): δ = 0.91 (s, 3 H, CH<sub>3</sub>), 1.07 (s, 3 H, CH<sub>3</sub>), 1.35 (s, 3 H, CH<sub>3</sub>), 1.80-2.00 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>), 2.18-2.33 (m, 1 H, CH<sub>2</sub>CH<sub>2</sub>), 2.45-2.70 (m, 3 H, NCH<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>), 3.89-3.96 (m, 2 H, NCH<sub>2</sub>), 3.99 (d, *J* = 11.0 Hz, 1 H, CH<sub>2</sub>O), 4.19 (dd, *J* = 11.0/2.2 Hz, 1 H, H<sub>2</sub>O), 5.11-5.20 (m, 1 H, NCH=CH), 6.71-6.79 (m, 1 H, NCH=).

### Preparation Example 3

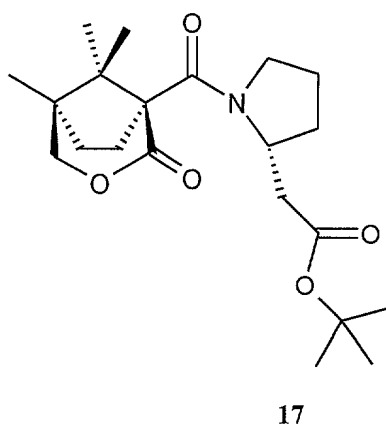
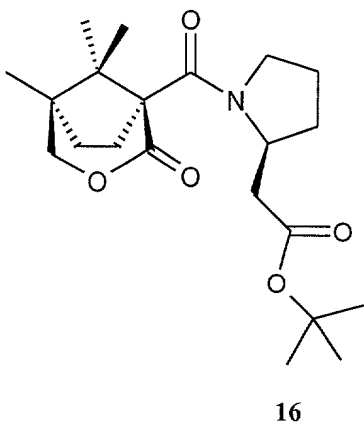
#### (a) Electrophilic $\alpha$ -Amidoalkylation, General Procedure

At  $-85\text{ }^{\circ}\text{C}$  gaseous HCl was introduced into anhydrous  $\text{CH}_2\text{Cl}_2$  (1 ml per 0.1 mmol of **14**) over a period of 20 min. Enamide **14**, dissolved in  $\text{CH}_2\text{Cl}_2$  (0.5 ml per 0.1 mmol), was then slowly added dropwise under strong stirring. The introduction of gaseous HCl was not stopped and was continued for 10 - 20 min. Thereafter excess HCl gas was removed for 1 h at  $-78\text{ }^{\circ}\text{C}$  in high vacuum. Then a solution of the respective organometallic reagent was added dropwise to the obtained reaction mixture. After the indicated reaction time hydrolysis ( $\text{H}_2\text{O}$ ) was effected at  $-78\text{ }^{\circ}$ . After the phases had separated the aqueous phase was extracted four times with  $\text{CH}_2\text{Cl}_2$ , and the organic phases were washed with saturated NaCl solution, dried with  $\text{MgSO}_4$  and concentrated in vacuo. The isolated residue was treated further as indicated.

#### (b) Preparation of

(1,1-Dimethylethyl)-{(2*S*)-*N*-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octan-1-yl-carbonyl]pyrrolidin-2-yl}acetate (**16**) and

(1,1-Dimethylethyl)-{(2*R*)-*N*-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octan-1-yl-carbonyl]pyrrolidin-2-yl}acetate (**17**)



Preparation of the reagent:

1.5 ml (2.4 mmol) of *n*-butyllithium (1.6 M in hexane) was added dropwise to a solution of 315  $\mu$ l (2.4 mmol) of diisopropylamine in 2.4 ml of anhydrous THF at -78 °C. After 30 min of stirring 320  $\mu$ l (2.4 mmol) of *tert*-butyl acetate was added. Stirring was continued for 40 min, with heating up to -30 °C. Thereafter 2.4 ml (2.4 mmol) of diethyl aluminumchloride solution (1 M in hexane) was added and again stirred for 20 min. The entire amount of reagent was used.

Electrophilic  $\alpha$ -amidoalkylation, general procedure: 0.158 g (0.6 mmol) of **14**, 6.6 ml (= 4 eq.) of organometallic reagent (see above), 16 h, -78 °C. CC (petrol ether/ethyl acetate = 7/3) afforded 203 mg (89.1 %) of **16** and **17** as mixture of diastereomers. HPLC analysis (column B; heptane/ethyl acetate = 80/20; 1.5 ml/min): **16**:  $t_{\text{ret}}$  = 16.1 min, 81.2%; **17**:  $t_{\text{ret}}$  = 20.4 min, 18.8%. Separation was effected by preparative HPLC (*n*-heptane / ethyl acetate = 82/18; 13.5 ml/min; **16**:  $t_{\text{ret}}$  = 33.8 min; **17**:  $t_{\text{ret}}$  = 43.6 min).

**16**: Yield: 154 mg (67.6 %); colorless crystals, m.p.: 135 °C. –  $[\alpha]_{\text{D}}^{20} = +18.2$  ( $c = 1.07$ ,  $\text{CHCl}_3$ ). –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20 °C):  $\delta = 0.88$  (s, 3 H,  $\text{CH}_3$ ), 1.03 (s, 3 H,  $\text{CH}_3$ ), 1.35 (s, 3 H,  $\text{CH}_3$ ), 1.43 (s, 9 H,  $\text{C}(\text{CH}_3)_3$ ), 1.63-1.69 (m, 1 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 1.74-1.96 (m, 4 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ,  $\text{CH}_2\text{CH}_2$ ), 2.14-2.24 (m, 2 H,  $\text{CH}_2\text{CH}_2$ ), 2.31-2.43 (m, 2 H,  $\text{CH}_2\text{CH}_2$ ,  $\text{CH}_2\text{COO}$ ), 2.85 (dd,  $J = 15.5/3.8$  Hz, 1 H,  $\text{CH}_2\text{COO}$ ), 3.21 (td,  $J = 9.5/6.5$  Hz, 1 H,  $\text{NCH}_2$ ), 3.72 (ddd,  $J = 9.5/7.3/2.4$  Hz, 1 H,  $\text{NCH}_2$ ), 3.91 (d,  $J = 11.0$  Hz, 1 H,  $\text{CH}_2\text{OC=O}$ ), 4.12 (dd,  $J = 11.0/2.2$  Hz, 1 H  $\text{CH}_2\text{OC=O}$ ), 4.42 (qd,  $J = 8.1/3.8$  Hz, 1 H,  $\text{NCHC}$ ).

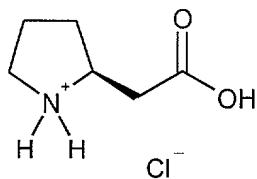
**17**: Yield: 36 mg (15.8 %); colorless crystals, m.p.: 89 °C.

$[\alpha]_{\text{D}}^{20} = +56.6$  ( $c = 1.1$ ,  $\text{CHCl}_3$ ). –  $^1\text{H}$  NMR ( $[\text{D}_5]\text{nitrobenzene}$ , 140 °C):  $\delta = 0.88$  (s, 3 H,  $\text{CH}_3$ ), 1.07 (s, 3 H,  $\text{CH}_3$ ), 1.35 (s, 3 H,  $\text{CH}_3$ ), 1.51 (s, 9 H,  $\text{C}(\text{CH}_3)_3$ ), 1.82-2.06 (m, 6 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ,  $\text{CH}_2\text{CH}_2$ ), 2.26 (ddd,  $J = 15.0/10.0/5.6$  Hz, 1 H,  $\text{CH}_2\text{CH}_2$ ), 2.35 (dd,  $J = 15.6/9.3$  Hz, 1 H,  $\text{CH}_2\text{COO}$ ), 2.61-2.72 (m, 1 H,  $\text{CH}_2\text{CH}_2$ ), 3.18 (dd,  $J = 15.6/3.7$  Hz, 1 H,  $\text{CH}_2\text{COO}$ ), 3.43-3.50 (m, 1 H,  $\text{NCH}_2$ ), 3.62 (dt,  $J = 10.6/6.9$  Hz, 1 H,  $\text{NCH}_2$ ), 3.92 (d,

$J = 11.1$  Hz, 1 H,  $\text{CH}_2\text{OC}=\text{O}$ ), 4.17 (dd,  $J = 11.1/2.0$  Hz, 1 H,  $\text{CH}_2\text{OC}=\text{O}$ ), 4.60-4.67 (m, 1 H, NCHC).

#### Preparation Example 4

##### (S)-2-Pyrrolidinoacetic acid (S-18-HCl)



**S-18-HCl**

325 mg (0.87 mmol) of **16** were dissolved in 4 ml of conc. acetic acid, 6 ml of conc. HCl were added thereto, and heating in a pressure tube was conducted for 24 h at 160 °C. Subsequently the reaction mixture was cautiously poured onto 15 ml of ice water and extracted several times with  $\text{CH}_2\text{Cl}_2$ . The combined  $\text{CH}_2\text{Cl}_2$  extracts were dried ( $\text{MgSO}_4$ ) and concentrated i. vac.. The yield of auxiliary was 131 mg (71 %). The aqueous phase was concentrated i. vac. and brought to dryness in high vacuum. The yield of pyrrolidinoacetic acid hydrochloride was 102 mg (70.8 %). For the determination of rotation and melting point a recrystallization from acetone/ methanol/ $\text{Et}_2\text{O}$  was carried out. Colorless crystals, m.p.: 173-175 °C,  $[\alpha]_{\text{D}}^{23} = +19.1$  (c = 1.2,  $\text{H}_2\text{O}$ ) Lit.: [T. Govindachari, T. Rajagopalan, N. Viswanathan, *J. Chem. Soc. Perkin Trans. 1*, **1974**, 1161-1165.] 175-176 °C,  $[\alpha]_{\text{D}}^{28} = +19.3$  (c = 1.74,  $\text{H}_2\text{O}$ ).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 20 °C):  $\delta$  = 1.66-1.79 (m, 1 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 1.92-2.16 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 2.21-2.32 (m, 1 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 2.74-2.92 (m, 2 H,  $\text{CH}_2\text{COO}$ ), 3.26-3.34 (m, 2 H,  $\text{NCH}_2$ ), 3.79-3.89 (m, 1 H, NCHC).

### Preparation Example 5

#### (S)-Pyrrolidin-2-yl-acetic acid methyl ester hydrochloride (S-19-HCl)

At 0 °C, 0.3 ml (4.2 mmol) of thionyl chloride was added dropwise to 1.2 ml of methanol. Thereafter 173 mg (1.05 mmol) of (S)-homoproline hydrochloride (**S-18-HCl**, see Preparation Example 4) was added. The reaction mixture was slowly heated to room temperature and stirred for 24 h at room temperature. Thereafter concentration in an aspirator vacuum and drying of the residue in high vacuum were conducted. Yield 176 mg (93.8 %) of colorless crystals. M.p.: 53 °C.  $[\alpha]_D^{20} = +3.3$  (c = 1.2, CHCl<sub>3</sub>) lit.: [T. Govindachari, T. Rajagopalan, N. Viswanathan, *J. Chem. Soc. Perkin Trans. 1* **1974**, 1161.]  $[\alpha]_D^{20} = +3.4$  (c = 2.0, CHCl<sub>3</sub>). – MS (70 eV); *m/z* (%): 143 (33) [M<sup>+</sup>], 128 (29), 115 (53), 110 (100).

### Preparation Example 6

#### (R)-1-Benzyloxycarbonylpyrrolidin-2-yl-acetic acid methyl ester (R-21)

The synthesis was conducted according to lit. (J.-M. Casal, A. Fürst, W. Meier, *Helv. Chim. Acta* **1976**, 59,1917-1924.), starting from 249 mg (1 mmol) of (R)-1-benzyloxycarbonylproline (**R-20**) via (R)-2-diazoacetylpyrrolidine-1-carboxylic acid benzyl ester. Yield: 113 mg (40.8%); colorless oil.

### Preparation Example 7

#### (S)-N-Benzyloxycarbonylproline methyl ester (S-22)

The synthesis was conducted according to lit.: R. Nurdinov, E. Liepin'sh, I. Kalvin'sh, *Chem. Heterocycl. Compd.* **1993**, 29, 1352- 1357. Batch size: 15 mmol (2.48 g); yield: 3.79 g (96%); colorless oil.

## Preparation Example 8

### (*R*)-*N*-Benzyloxycarbonylproline methyl ester (**R-22**)

The synthesis was conducted according to the procedure for **S-22**. Batch size: 9.17 mmol (1.52 g); yield: 2.31 g (96%); colorless oil.

## Preparation Example 9

### (*2E*)-3-[(*2S*)-1-(Benzyloxycarbonyl)pyrrolidin-2-yl]acrylic acid methyl ester and (*2Z*)-3-[(*2S*)-1-(Benzyloxycarbonyl)pyrrolidin-2-yl] acrylic acid methyl ester (**S-24**)

The synthesis was conducted according to lit.. [R. Grote, A. Zeeck, J. Stümpfel, H. Zähler, *Liebigs Ann. Chem.* **1990**, 29, 525-530; T. Sato, K. Tsujimoto, K. Matsubayashi, H. Ishibashi, M. Ikeda, *Chem. Pharm. Bull.* **1992**, 40, 2308-2312. ]

At -60 °C, 18 ml of DIBAH solution (1 M in hexane) was added dropwise to a solution of 2.346 g (8.92 mmol) of **S-22** in 50 ml toluene over 15 min, and the reaction mixture was stirred for 1 h at -60 °C. Subsequently the reaction was stopped by dropwise addition of 2 ml of methanol, heated to RT and taken up in 1 N HCl and Et<sub>2</sub>O. The aqueous phase was extracted three times with Et<sub>2</sub>O, and the combined organic phases were dried (MgSO<sub>4</sub>) and concentrated i. vac.. The oily residue (2.07 g) was dissolved in 35 ml of acetonitrile, and 454 mg (10.7 mmol, 1.2 equiv.) of LiCl and 1.86 ml (10.7 mmol, 1.2 equiv.) of DIPEA were added thereto. Thereafter 1.73 ml (10.7 mmol, 1.2 equiv.) of trimethylphosphonoacetate was added dropwise. The reaction mixture was stirred for 16 h at RT, then concentrated i. vac., taken up with Et<sub>2</sub>O and water, and the aqueous phase was extracted three times with Et<sub>2</sub>O. The combined organic phases were dried (MgSO<sub>4</sub>) and concentrated i. vac.. CC (petrol ether/ethyl acetate = 7/3) afforded 1.88 g (72.9%) of a colorless oil.

### Preparation Example 10

**(2E)-3-[(2R)-1-(Benzyloxycarbonyl)pyrrolidin-2-yl]acrylic acid methyl ester and  
(2Z)-3-[(2R)-1-(Benzyloxycarbonyl)pyrrolidin-2-yl]acrylic acid methyl ester (R-24)**

The synthesis was conducted according to the procedure for **S-24**. Batch size: 7.03 mmol (1.85 g); yield: 1.48 g (72.8%); colorless oil.

### Preparation Example 11

**(S)-Proline methyl ester hydrochloride (S-25-HCl)**

The synthesis was conducted according to lit.: D. Hoogwater, M. Peereboom, *Tetrahedron* **1990**, 46, 5325-5332; J. Pastuszak, J. Gardener, J. Singh und D. Rich, *J. Org. Chem.* **1982**, 47, 2982-2987. Batch size: 43.5 mmol (5.02 g); yield: 6.8 g (94%); m.p.: 72 °C (lit.: 73 °C).

### Preparation Example 12

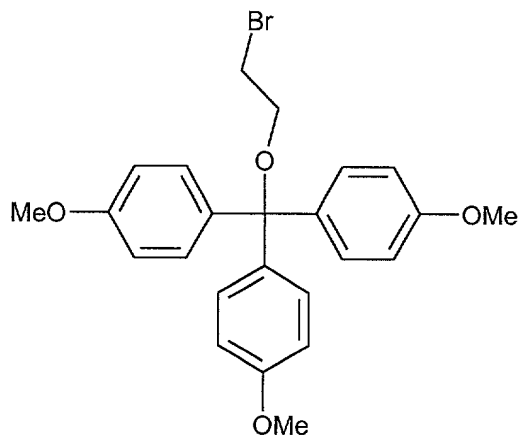
**(R)-Proline methyl ester hydrochloride (R-25-HCl)**

The synthesis was conducted according to lit.: D. Hoogwater, M. Peereboom, *Tetrahedron* **1990**, 46, 5325-5332; J. Pastuszak, J. Gardener, J. Singh und D. Rich, *J. Org. Chem.* **1982**, 47, 2982-2987. Batch size: 43.5 mmol (5.02 g); yield: 7.0 g (97%); m.p.: 71 °C (lit. 73 °C).



### Preparation Example 13

#### 2-[(Trismethoxyphenyl)methoxy]ethyl bromide (R-Br c)



**R-Br c**

50  $\mu$ l of conc.  $\text{H}_2\text{SO}_4$  was added dropwise to a solution of 1.05 g (3 mmol) of tris-(4-methoxyphenyl)methanol in 5 ml of benzene, and the reaction mixture was heated to 65  $^\circ\text{C}$  for 5 min. Upon the addition of 318  $\mu$ l (4.5 mmol) of bromoethanol the reaction mixture was stirred for additional 60 min at RT. Then it was taken up in  $\text{Et}_2\text{O}$  and water, the aqueous phase was extracted three times with  $\text{Et}_2\text{O}$ , dried ( $\text{MgSO}_4$ ) and concentrated i. vac.. CC (petrol ether/ $\text{Et}_2\text{O}$  = 9/1) of the oily residue afforded 464 mg (33.8%) of a colorless oil. Additionally 564 mg (53.7%) of tris(4-methoxyphenyl)methanol could be recovered.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20  $^\circ\text{C}$ ):  $\delta$  = 3.37-3.46 (m, 4 H,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 3.79 (s, 9 H,  $\text{OCH}_3$ ), 6.81-6.86 (m, 6 H, aromat. H), 7.32-7.37 (m, 6 H, aromat. H).

## Example 1

### (a) N-Alkylation of the pyrrolidinylalkane carboxylic acid esters

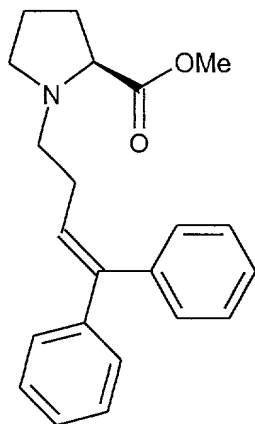
#### General Procedure A

To a suspension of the hydrochloride of the indicated pyrrolidinylalkanecarboxylic acid ester (1 equiv.), 0.1 equiv. of potassium iodide and 2 equiv. of potassium carbonate in acetone (1.5 ml/mmol), 1 equiv. of the indicated bromide, dissolved in acetone (1 ml/mmol) was added dropwise. The mixture was stirred at room temperature for the indicated time, taken up in water and  $\text{CH}_2\text{Cl}_2$ , extracted three times with  $\text{CH}_2\text{Cl}_2$ , dried ( $\text{MgSO}_4$ ) and concentrated i. vac.. The isolated residue was treated further as indicated.

#### General Procedure B

To a solution of the indicated Cbz-protected amino acid alkyl ester (= 1 equiv.) in MeOH (0.1 M) was added a spatula tip full of Pd/C and the solution was stirred under  $\text{H}_2$  atmosphere at normal pressure (balloon) for 1 h at RT. After the catalyst had been filtered off a concentration i. vac. was conducted, and the obtained residue was suspended in acetone (1.5 ml/mmol) with 1 equiv. of potassium carbonate and 0.1 equiv. of potassium iodide. Subsequently 1 equiv. of the indicated bromide, dissolved in acetone (1 ml/mmol), was added dropwise. The mixture was stirred at room temperature for the indicated time, taken up in water and  $\text{CH}_2\text{Cl}_2$ , extracted three times with  $\text{CH}_2\text{Cl}_2$ , dried ( $\text{MgSO}_4$ ) and concentrated i. vac.. The isolated residue was treated further as indicated.

(b) (S)-N-(4,4-Diphenylbut-3-en-1-yl)pyrrolidine-2-carboxylic acid methyl ester (S-27a)



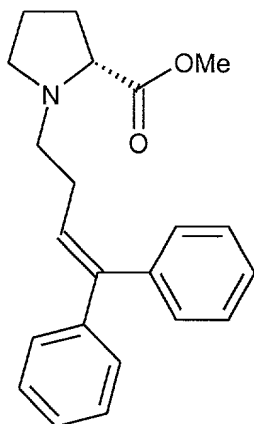
S-27a

N-Alkylation of the pyrrolidinyllalkanecarboxylic acid alkyl esters:

General Procedure A: 497 mg (3 mmol) of L-proline methyl ester hydrochloride (**S-25-HCl**, see Preparation Example 11), 49.8 mg (0.3 mmol) of potassium iodide, 829 mg (6 mmol) of potassium carbonate, 861 mg (3 mmol) of 4,4-diphenylbut-3-en-1-yl bromide. Reaction time: 46 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 527 mg (52.4 %) of a colorless oil.

$[\alpha]_D^{20} = -35.7$  ( $c = 2.79$ ,  $\text{CHCl}_3$ ). –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20 °C):  $\delta = 1.70\text{--}1.85$  (m, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 1.85–1.96 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 2.02–2.14 (m, 1 H,  $\text{NCHCCH}_2$ ), 2.27–2.37 (m, 3 H,  $\text{NCH}_2$ ,  $=\text{CCH}_2\text{CH}_2\text{N}$ ), 2.49–2.57 (m, 1 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ), 2.81 (dt,  $J = 11.5/8.1\text{ Hz}$ , 1 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ), 3.11 (td,  $J = 8.1/3.0\text{ Hz}$ , 1 H,  $\text{NCH}_2$ ), 3.16 (dd,  $J = 8.7/5.9\text{ Hz}$ , 1 H,  $\text{NCHCOO}$ ), 3.68 (s, 3 H,  $\text{OCH}_3$ ), 6.08 (t,  $J = 7.4\text{ Hz}$ , 1 H,  $=\text{CH}$ ), 7.15–7.40 (m, 10 H, aromat. H).

(c) (*R*)-N-(4,4-Diphenylbut-3-en-1-yl)pyrrolidine-2-carboxylic acid methyl ester (**R-27a**)

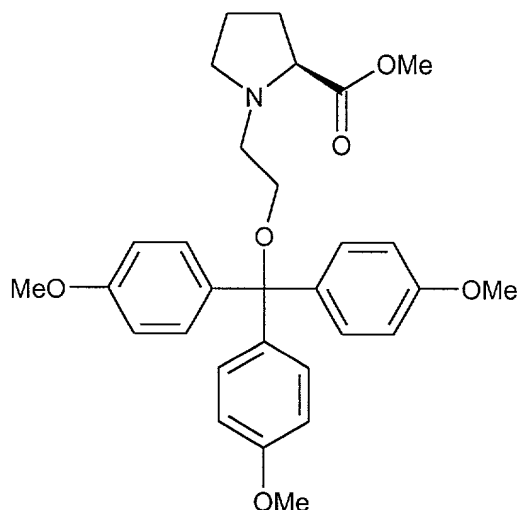


**R-27a**

N-Alkylation of the pyrrolidinyllalkanecarboxylic acid alkyl esters:

General Procedure A: 359 mg (2.17 mmol) of D-proline methyl ester hydrochloride (**R-25-HCl**, see Preparation Example 12), 36 mg (0.217 mmol) of potassium iodide, 600 mg (4.34 mmol) of potassium carbonate, 623 mg (2.17 mmol) of 4,4-diphenylbut-3-en-1-yl bromide. Reaction time: 48 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 350 mg (48.1 %) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-27a**.  $[\alpha]_{\text{D}}^{20} = +34.9$  ( $c = 1.72$ ,  $\text{CHCl}_3$ ).

(d) (*S*)-N-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidine-2-carboxylic acid methyl ester (**S-27c**)

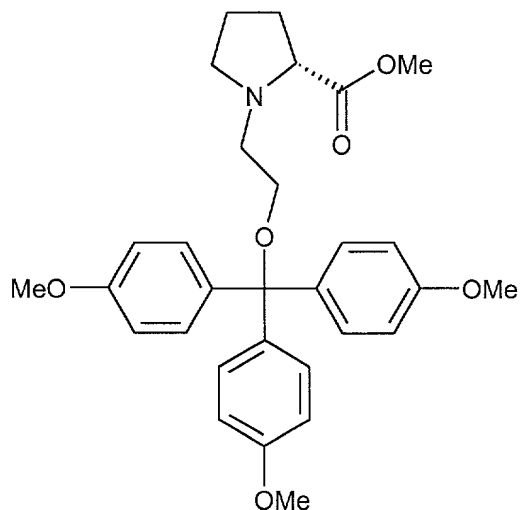


**S-27c**

N-Alkylation of the pyrrolidinyllalkanecarboxylic acid alkyl esters:

General Procedure A: 248 mg (1.5 mmol) of L-proline methyl ester hydrochloride (**S-25-HCl**, see Preparation Example 11), 24.9 mg (0.15 mmol) of potassium iodide, 415 mg (3 mmol) of potassium carbonate, 686 mg (1.5 mmol) of **R-Br c** (see Preparation Example 13). Reaction time: 40 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 285 mg (37.6 %) of a colorless oil.  $[\alpha]_D^{20} = -29.6$  (c = 1.05,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20 °C):  $\delta$  = 1.73-1.81 (m, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 1.81-1.93 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 2.02-2.14 (m, 1 H,  $\text{NCHCCH}_2$ ), 2.43 (q,  $J$  = 8.7 Hz, 1 H,  $\text{NCH}_2$ ), 2.73 (dt,  $J$  = 12.6/6.3 Hz, 1 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ), 2.95 (dt,  $J$  = 12.6/6.3 Hz, 1 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ), 3.09-3.16 (m, 1 H,  $\text{NCH}_2$ ), 3.21 (t,  $J$  = 6.3 Hz, 2 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ), 3.26 (dd,  $J$  = 8.9/5.8 Hz, 1 H,  $\text{NCHCOO}$ ), 3.65 (s, 3 H,  $\text{COOCH}_3$ ), 3.78 (s, 9 H,  $\text{OCH}_3$ ), 6.79-6.83 (m, 6 H, aromat. H), 7.29-7.34 (m, 6 H, aromat. H).

(e) (*R*)-N-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidine-2-carboxylic acid methyl ester (**R-27c**)

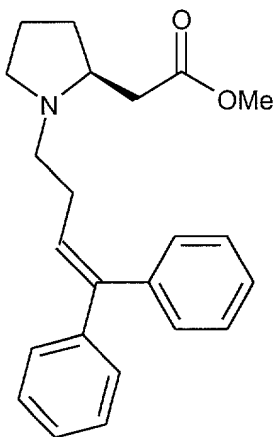


**R-27c**

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure A: 331 mg (2.0 mmol) of D-proline methyl ester hydrochloride (**R-25-HCl**, see Preparation Example 12), 33.2 mg (0.2 mmol) of potassium iodide, 553 mg (4.0 mmol) of potassium carbonate, 914 mg (2.0 mmol) of **R-Br c** (see Preparation Example 13). Reaction time: 40 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 395 mg (39.1 %) of a colorless oil. The analytical data ( $^1\text{H}$  NMR, IR, MS) of the compound is in agreement with that of the (*S*)-enantiomer **S-27c**.  $[\alpha]_{\text{D}}^{20} = +30.5$  ( $c = 1.75$ ,  $\text{CHCl}_3$ ).

(f) (*S*)-[1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidine-2-yl]acetic acid methyl ester (**S-28a**)



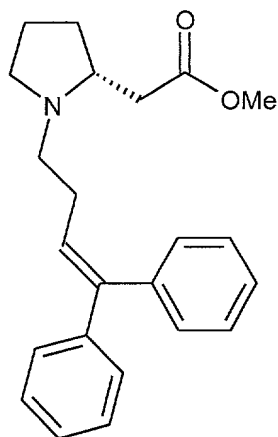
**S-28a**

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure A: 176 mg (0.983 mmol) of (*S*)-pyrrolidin-2-ylacetic acid methyl ester hydrochloride (**S-19-HCl**, see Preparation Example 5), 16.6 mg (0.1 mmol) of potassium iodide, 304 mg (2.2 mmol) of potassium carbonate, 287 mg (1 mmol) of 4,4-diphenylbut-3-en-1-yl bromide. Reaction time: 46 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 218 mg (63.5 %) of a colorless oil.

$[\alpha]_D^{20} = -62.5$  ( $c = 3.35$ ,  $\text{CHCl}_3$ ). –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20 °C):  $\delta = 1.49\text{--}1.59$  (m, 1 H,  $\text{NCHCCH}_2$ ), 1.62–1.80 (m, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 1.94–2.05 (m, 1 H,  $\text{NCHCCH}_2$ ), 2.11 (dt,  $J = 8.2/9.0$  Hz, 1 H,  $\text{NCH}_2$ ), 2.26 (dd,  $J = 14.9/9.0$  Hz, 1 H,  $\text{CH}_2\text{COO}$ ), 2.28–2.35 (m, 3 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ), 2.60 (dd,  $J = 14.9/4.3$  Hz, 1 H,  $\text{CH}_2\text{COO}$ ), 2.70–2.79 (m, 1 H,  $\text{NCHC}$ ), 2.80–2.88 (m, 1 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ), 3.02 (ddd,  $J = 9.3/7.5/3.1$  Hz, 1 H,  $\text{NCH}_2$ ), 3.64 (s, 3 H,  $\text{OCH}_3$ ), 6.10 (t,  $J = 7.0$  Hz, 1 H,  $=\text{CH}$ ), 7.16–7.40 (m, 10 H, aromat. H).

(g) (*R*)-[1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl]acetic acid methyl ester (**R-28a**)



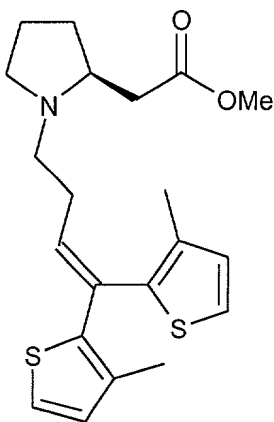
**R-28a**

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 227 mg (0.82 mmol) of (*R*)-1-benzyloxycarbonylpyrrolidin-2-ylacetic acid methyl ester (**R-21**, see Preparation Example 6), 13.6 mg (0.082 mmol) of potassium iodide, 113 mg (0.82 mmol) of potassium carbonate, 235 mg (0.82 mmol) of 4,4-diphenylbut-3-en-1-yl bromide. Reaction time: 47 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 175 mg (61.1 %) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-28a**.  $[\alpha]_{\text{D}}^{20} = +61.2$  ( $c = 1.49$ ,  $\text{CHCl}_3$ ).



(h) (*S*)-{1-[4,4-Bis(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidin-2-yl}acetic acid methyl ester (**S-28b**)



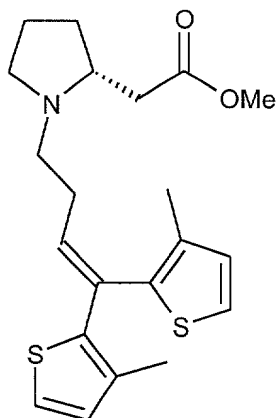
**S-28b**

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure A: 179 mg (1.0 mmol) of (*S*)-pyrrolidin-2-yl acetic acid methyl ester hydrochloride (**S-19-HCl**, see Preparation Example 5), 16.6 mg (0.1 mmol) of potassium iodide, 276 mg (2.0 mmol) of potassium carbonate, 327 mg (1.0 mmol) of 4,4-bis(3-methyl-2-thienyl)but-3-en-1-yl bromide. Reaction time: 46 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 159 mg (40.8 %) of a colorless oil.

$[\alpha]_D^{20} = -60.2$  ( $c = 0.99$ ,  $\text{CHCl}_3$ ). –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20 °C):  $\delta = 1.49\text{--}1.57$  (m, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 1.67–1.76 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 1.96–2.03 (m, 1 H,  $\text{NCHCCH}_2$ ), 2.02 (s, 3 H,  $-\text{CH}_3$ ), 2.04 (s, 3 H,  $-\text{CH}_3$ ), 2.13 (td,  $J = 8.7/8.4$  Hz, 1 H,  $\text{NCH}_2$ ), 2.25 (dd,  $J = 14.8/8.8$  Hz, 1 H,  $\text{CH}_2\text{COO}$ ), 2.28–2.36 (m, 3 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ), 2.62 (dd,  $J = 14.8/4.4$  Hz, 1 H,  $\text{CH}_2\text{COO}$ ), 2.70–2.78 (m, 1 H,  $\text{NCHC}$ ), 2.81–2.89 (m, 1 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ), 3.04 (ddd,  $J = 10.0/7.4/3.3$  Hz, 1 H,  $\text{NCH}_2$ ), 3.66 (s, 3 H,  $-\text{OCH}_3$ ), 6.06 (t,  $J = 7.0$  Hz, 1 H,  $=\text{CH}$ ), 6.77 (d,  $J = 5.2$  Hz, 1 H,  $\text{SC}=\text{CH}$ ), 6.84 (d,  $J = 5.2$  Hz, 1 H,  $\text{SC}=\text{CH}$ ), 7.06 (d,  $J = 5.2$  Hz, 1 H,  $\text{SCH}=\text{}$ ), 7.21 (d,  $J = 5.2$  Hz, 1 H,  $\text{SCH}=\text{}$ ).

(i) (*R*)-{1-[4,4-Bis(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidin-2-yl}acetic acid methyl ester (**R-28b**)



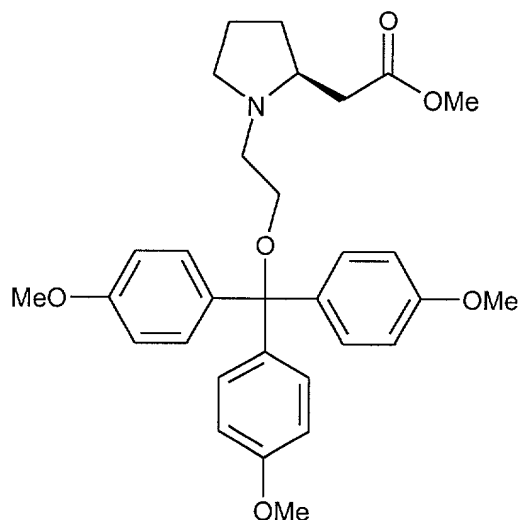
**R-28b**

N-Alkylation of the pyrrolidinyllalkanecarboxylic acid alkyl esters:

General Procedure B: 277 mg (1.0 mmol) of (*R*)-1-benzyloxycarbonylpyrrolidin-2-yl acetic acid methyl ester (**R-21**, see Preparation Example 6), 16.6 mg (1.0 mmol) of potassium iodide, 138 mg (1.0 mmol) of potassium carbonate, 327 mg (1 mmol) of 4,4-bis-(3-methyl-2-thienyl)but-3-en-1-yl bromide. Reaction time: 46 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 161 mg (41.3 %) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-28b**.

$[\alpha]_{\text{D}}^{20} = +61.3$  ( $c = 1.04$ ,  $\text{CHCl}_3$ ).

(j) **(S)-(1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl)acetic acid methyl ester (S-28c)**



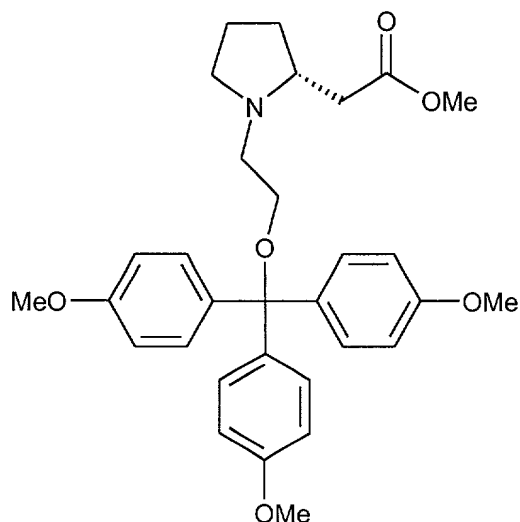
**S-28c**

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure A: 215 mg (1.2 mmol) of (*S*)-pyrrolidin-2-ylacetic acid methyl ester hydrochloride (**S-19-HCl**, see Preparation Example 5), 19.9 mg (0.12 mmol) of potassium iodide, 332 mg (2.4 mmol) of potassium carbonate, 548 mg (1 mmol) of **R-Br c** (see Preparation Example 13). Reaction time: 46 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 220 mg (35.2 %) of a colorless oil.

$[\alpha]_D^{20} = -27.6$  ( $c = 1.77$ ,  $\text{CHCl}_3$ ). –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20 °C):  $\delta = 1.49\text{--}1.59$  (m, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 1.68–1.80 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 1.97–2.07 (m, 1 H,  $\text{NCHCCH}_2$ ), 2.21–2.31 (m, 2 H,  $\text{CH}_2\text{COO}$ ,  $\text{NCH}_2$ ), 2.51 (dt,  $J = 12.5/6.5$  Hz, 1 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ), 2.65 (dd,  $J = 15.1/4.0$  Hz, 1 H,  $\text{CH}_2\text{COO}$ ), 2.79–2.87 (m, 1 H,  $\text{NCHC}$ ), 2.97 (dt,  $J = 12.5/6.5$  Hz, 1 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ), 3.06 (ddd,  $J = 10.4/7.1/3.5$  Hz, 1 H,  $\text{NCH}_2$ ), 3.20 (m, 2 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ), 3.67 (s, 3 H,  $\text{COOCH}_3$ ), 3.81 (s, 9 H,  $-\text{OCH}_3$ ), 6.81–6.87 (m, 6 H, aromat. H), 7.34–7.39 (m, 6 H, aromat. H).

(k) (*R*)-(1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl)acetic acid methyl ester (**R-28c**)

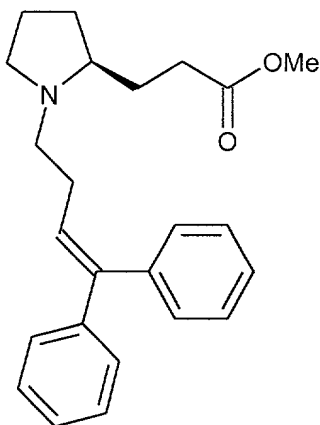


**R-28c**

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 227 mg (0.82 mmol) of (*R*)-1-benzyloxycarbonylpyrrolidin-2-ylacetic acid methyl ester (**R-21**, see Preparation Example 6), 13.6 mg (0.082 mmol) of potassium iodide, 113 mg (0.82 mmol) of potassium carbonate, 375 mg (0.82 mmol) of **R-Br c** (see Preparation Example 13). Reaction time: 45 h. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-28c**. Purification by column chromatography (petrol ether/ethyl acetate = 20/80) afforded 175 mg (41.1 %) of a colorless oil.  $[\alpha]_{\text{D}}^{20} = +26.7$  ( $c = 1.5$ ,  $\text{CHCl}_3$ ).

(l) 3-[(*S*)-1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl] propionic acid methyl ester  
(S-29a)



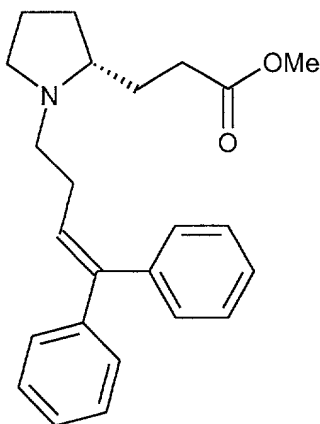
S-29a

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 269 mg (0.93 mmol) of **S-24** (see Preparation Example 9), 15.4 mg (0.093 mmol) of potassium iodide, 128 mg (0.93 mmol) of potassium carbonate, 267 mg (0.93 mmol) of 4,4-diphenylbut-3-en-1-yl bromide. Reaction time: 48 h. Purification by column chromatography (*n*-hexane/ether = 7/3) afforded 142 mg (42.0 %) of a colorless oil.

$[\alpha]_D^{20} = -63.9$  ( $c = 1.1$ ,  $\text{CHCl}_3$ ). –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20 °C):  $\delta = 1.30\text{--}1.39$  (m, 1 H,  $\text{NCHCCH}_2$ ), 1.47–1.70 (m, 3 H,  $\text{CH}_2\text{CH}_2\text{COO}$ ,  $\text{NCH}_2\text{CH}_2$ ), 1.75–1.83 (m, 1 H,  $\text{NCHCCH}_2$ ), 1.83–1.93 (m, 1 H,  $\text{CH}_2\text{CH}_2\text{COO}$ ), 1.99 (td,  $J = 9.0/8.2$  Hz, 1 H,  $\text{NCH}_2$ ), 2.11–2.28 (m, 5 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ,  $\text{CH}_2\text{COO}$ ,  $\text{NCHC}$ ), 2.33 (ddd,  $J = 15.6/9.5/5.9$  Hz, 1 H,  $\text{CH}_2\text{COO}$ ), 2.84 (ddd,  $J = 15.3/8.5/6.1$  Hz, 1 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ), 2.97 (ddd,  $J = 9.0/7.4/2.9$  Hz, 1 H,  $\text{NCH}_2$ ), 3.59 (s, 3 H,  $\text{OCH}_3$ ), 6.05 (t,  $J = 7.3$  Hz, 1 H,  $=\text{CH}$ ), 7.10–7.33 (m, 10 H, aromat. H).

(m) 3-[(*R*)-1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl]propionic acid methyl ester  
(**R-29a**)

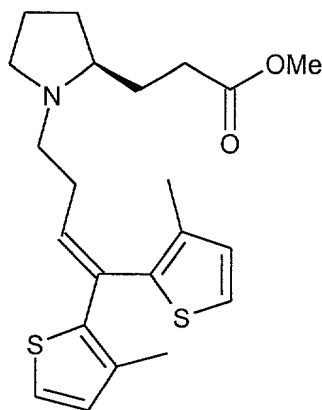


**R-29a**

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 231 mg (0.8 mmol) **R-24** (see Preparation Example 10), 13.3 mg (0.08 mmol) of potassium iodide, 111 mg (0.8 mmol) of potassium carbonate, 230 mg (0.8 mmol) of 4,4-diphenylbut-3-en-1-yl bromide. Reaction time: 46 h. Purification by column chromatography (*n*-hexane/ether = 3/7) afforded 131 mg (45.0 %) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-29a**.  $[\alpha]_{\text{D}}^{20} = +63.55$  ( $c = 1.07$ ,  $\text{CHCl}_3$ ).

(n) 3-[(*S*)-1-[4,4-Bis(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidin-2-yl]propionic acid methyl ester (**S-29b**)

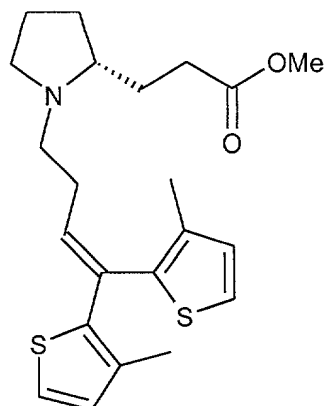


**S-29b**

N-Alkylation of the pyrrolidinyllalkanecarboxylic acid alkyl esters:

General Procedure B: 289 mg (1.0 mmol) of **S-24** (see Preparation Example 9), 16.6 mg (0.1 mmol) of potassium iodide, 138 mg (1.0 mmol) of potassium carbonate, 327 mg (1.0 mmol) of 4,4-bis(3-methyl-2-thienyl)but-3-en-1-yl bromide. Reaction time: 46 h. Purification by column chromatography (petrol ether/ethyl acetate = 5/5) afforded 165 mg (40.9 %) of a colorless oil.  $[\alpha]_D^{20} = -6.2$  ( $c = 1.05$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20 °C):  $\delta = 1.37$ - $1.47$  (m, 1 H,  $\text{NCHCCH}_2$ ),  $1.53$ - $1.78$  (m, 3 H,  $\text{CH}_2\text{CH}_2\text{COO}$ ,  $\text{NCH}_2\text{CH}_2$ ),  $1.82$ - $1.90$  (m, 1 H,  $\text{NCHCCH}_2$ ),  $1.91$ - $2.01$  (m, 1 H,  $\text{CH}_2\text{CH}_2\text{COO}$ ),  $2.03$  (s, 3 H,  $\text{CH}_3$ ),  $2.05$  (s, 3 H,  $\text{CH}_3$ ),  $2.07$  (q,  $J = 8.9$  Hz, 1 H,  $\text{NCH}_2$ ),  $2.18$ - $2.35$  (m, 5 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ,  $\text{CH}_2\text{COO}$ ,  $\text{NCHC}$ ),  $2.40$  (ddd,  $J = 15.6/9.5/5.9$  Hz, 1 H,  $\text{CH}_2\text{COO}$ ),  $2.91$  (dt,  $J = 11.4/8.1$  Hz, 1 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ),  $3.07$  (ddd,  $J = 9.5/7.5/3.0$  Hz, 1 H,  $\text{NCH}_2$ ),  $3.68$  (s, 3 H,  $\text{OCH}_3$ ),  $6.09$  (t,  $J = 7.3$  Hz, 1 H,  $=\text{CH}$ ),  $6.77$  (d,  $J = 5.2$  Hz, 1 H,  $\text{SC}=\text{CH}$ ),  $6.85$  (d,  $J = 5.2$  Hz, 1 H,  $\text{SC}=\text{CH}$ ),  $7.06$  (d,  $J = 5.2$  Hz, 1 H,  $\text{SCH}=\text{}$ ),  $7.21$  (d,  $J = 5.2$  Hz, 1 H,  $\text{SCH}=\text{}$ ).

(o) 3-[(*R*)-1-[4,4-Bis(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidin-2-yl]propionic acid methyl ester (**R-29b**)

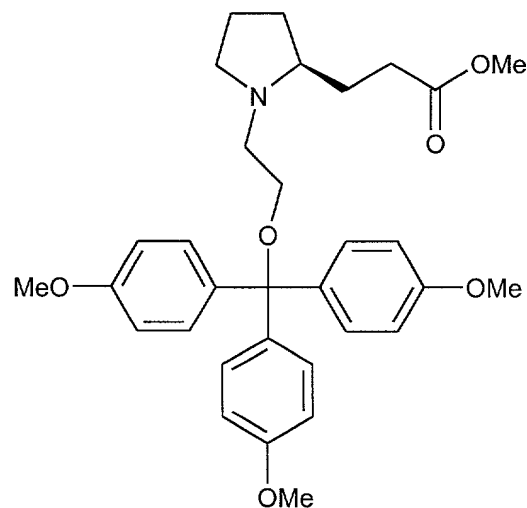


**R-29b**

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 474 mg (1.64 mmol) of **R-24** (see Preparation Example 10), 27.2 mg (0.16 mmol) of potassium iodide, 227 mg (1.64 mmol) of potassium carbonate, 536 mg (1.64 mmol) of 4,4-bis(3-methyl-2-thienyl)but-3-en-1-yl bromide. Reaction time: 47 h. Purification by column chromatography (petrol ether/ethyl acetate = 5/5) afforded 260 mg (39.4 %) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-29b**.  $[\alpha]_D^{20} = +6.3$  ( $c = 1.18$ ,  $\text{CHCl}_3$ ).

(p) 3-[(*S*)-1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]propionic acid methyl ester (**S-29c**)



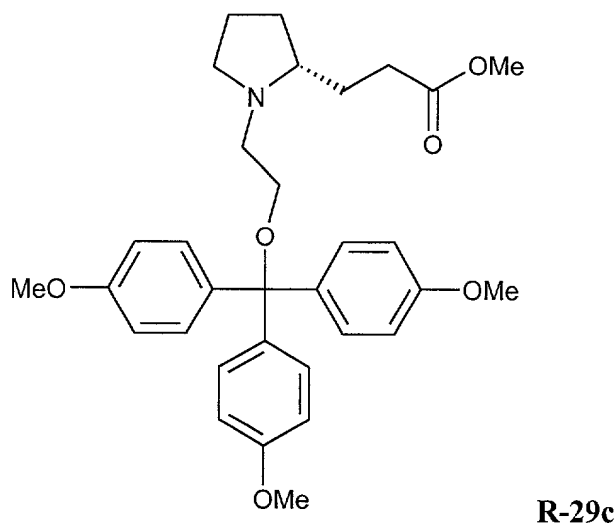
**S-29c**



N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 289 mg (1.0 mmol) of **S-24** (see Preparation Example 9), 16.6 mg (0.1 mmol) of potassium iodide, 138 mg (1.0 mmol) of potassium carbonate, 457 mg (1.0 mmol) of **R-Br c** (see Preparation Example 13). Reaction time: 48 h. Purification by column chromatography (petrol ether/ ethyl acetate = 2/8) afforded 117 mg (21.9 %) of a colorless oil.  $[\alpha]_D^{20} = -29.5$  ( $c = 1.27$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ,  $20^\circ\text{C}$ ):  $\delta = 1.36$ - $1.46$  (m, 1 H,  $\text{NCH}_2\text{CH}_2$ ),  $1.56$ - $1.64$  (m, 1 H,  $\text{CH}_2\text{CH}_2\text{COO}$ ),  $1.64$ - $1.73$  (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ),  $1.81$ - $1.89$  (m, 1 H,  $\text{NCHCCH}_2$ ),  $1.90$ - $2.00$  (m, 1 H,  $\text{CH}_2\text{CH}_2\text{COO}$ ),  $2.15$  (q,  $J = 9.0$  Hz, 1 H,  $\text{NCH}_2$ ),  $2.21$ - $2.47$  (m, 4 H,  $\text{CH}_2\text{COO}$ ,  $\text{OCH}_2\text{CH}_2\text{N}$ ,  $\text{NCHC}$ ),  $2.98$ - $3.10$  (m, 2 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ,  $\text{NCH}_2$ ),  $3.12$ - $3.25$  (m, 2 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ),  $3.67$  (s, 3 H,  $\text{COOCH}_3$ ),  $3.80$  (s, 9 H,  $\text{OCH}_3$ ),  $6.80$ - $6.85$  (m, 6 H, aromat. H),  $7.33$ - $7.37$  (m, 6 H, aromat. H).

(q) 3-[(*R*)-1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]propionic acid methyl ester (**R-29c**)



N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 289 mg (1.0 mmol) of **R-24** (see Preparation Example 10), 16.6 mg (0.1 mmol) of potassium iodide, 138 mg (1.0 mmol) of potassium carbonate, 457 mg (1.0 mmol) of **R-Br c** (see Preparation Example 13),. Reaction time: 48 h. Purification by

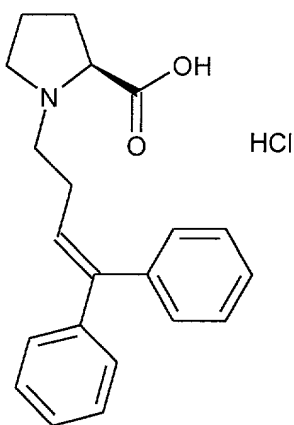
column chromatography (petrol ether/ethyl acetate = 2/8) afforded 239 mg (44.8%) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-29c**.  $[\alpha]_D^{20} = +29.5$  ( $c = 1.05$ ,  $\text{CHCl}_3$ ).

## Example 2

### (a) Saponification of the methyl esters, general procedure

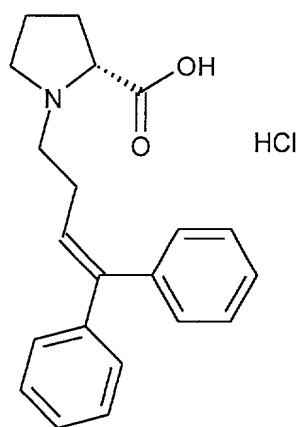
The methyl esters (= 1 equiv.) each were dissolved in ethanol (about 2 ml / mmol). The solution was cooled to 0 °C, and 12 N NaOH (2 equiv.) was added dropwise thereto. Then the cooling bath was removed and the reaction mixture was stirred at RT for the indicated period of time. Thereafter the reaction mixture was again cooled to 0 °C and, if not stated otherwise, acidified to pH  $\approx$  6 by dropwise addition of 0.25 N HCl. The reaction mixture was taken up in  $\text{CH}_2\text{Cl}_2$  and water and extracted five times with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were dried ( $\text{MgSO}_4$ ), concentrated i. vac., and the obtained residue was treated further as indicated.

### (b) (*S*)-N-(4,4-Diphenylbut-3-en-1-yl)pyrrolidine-2-carboxylic acid hydrochloride (**S-30a**)



Saponification of methyl ester, General Procedure: 265 mg (0.79 mmol) of **S-27a** (see Example 1(b)), 132  $\mu$ l of 12 M NaOH, reaction time 5 h. The work-up was conducted in deviation from the General Procedure by dropwise acidification with cooling with 4 M HCl to pH  $\approx$  1 and five extractions with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried (MgSO<sub>4</sub>), concentrated i. vac., and the obtained hydrochloride was recrystallized from ethanol. Yield: 231 mg (81.9%); colorless crystals, m.p.: 220 °C. –  $[\alpha]_D^{20} = -21.0$  (c = 1.00, CH<sub>3</sub>OH). – <sup>1</sup>H NMR (CD<sub>3</sub>OD, 20 °C):  $\delta$  = 1.88-2.00 (m, 1 H, NCH<sub>2</sub>CH<sub>2</sub>), 2.08-2.21 (m, 2 H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.43-2.53 (m, 1 H, NCHCCH<sub>2</sub>), 2.54-2.62 (m, 2 H, =CHCH<sub>2</sub>), 3.05-3.14 (m, 1 H, NCH<sub>2</sub>), 3.20-3.30 (m, 1 H, =CHCH<sub>2</sub>CH<sub>2</sub>), 3.45 (td,  $J$  = 12.4/8.0 Hz, 1 H, =CHCH<sub>2</sub>CH<sub>2</sub>), 3.62 (ddd,  $J$  = 12.4/7.5/4.0 Hz, 1 H, NCH<sub>2</sub>), 4.08 (dd,  $J$  = 9.6/6.8 Hz, 1 H, NCHC), 6.11 (t,  $J$  = 7.3 Hz, 1 H, =CH), 7.19-7.49 (m, 10 H, aromat. H).

**(c) (R)-N-(4,4-Diphenylbut-3-en-1-yl)pyrrolidine-2-carboxylic acid hydrochloride (R-30a)**

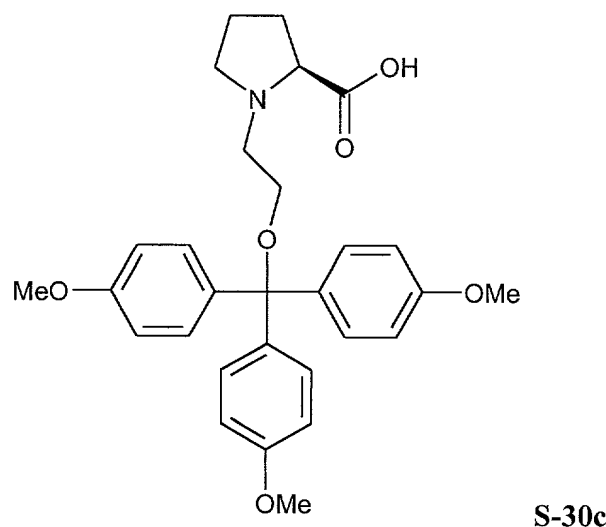


**R-30a**

Saponification of methyl ester, General Procedure: 210 mg (0.63 mmol) **R-27a** (see Example 1(c)), 105  $\mu$ l of 12 M NaOH, reaction time 5 h. The work-up was conducted in deviation from the General Procedure by dropwise acidification with cooling with 4 M HCl to pH  $\approx$  1 and five extractions with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were

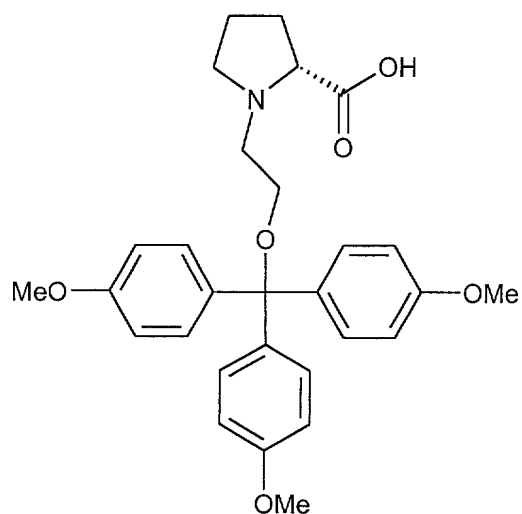
dried (MgSO<sub>4</sub>), concentrated i. vac., and the obtained hydrochloride was recrystallized from ethanol.. Yield: 184 mg (82.1%); colorless crystals, m.p.: 218 °C. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-30a**. –  $[\alpha]_{\text{D}}^{20} = +21.9$  ( $c = 0.71$ , CH<sub>3</sub>OH).

(d) (*S*)-N-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidine-2-carboxylic acid (**S-30c**)



Saponification of methyl ester, General Procedure: 289 mg (0.63 mmol) **S-27c** (see Example 1(d)), 95  $\mu$ l of 12 M NaOH, reaction time 4 h. Recrystallization from ether/*n*-pentane (1/1) afforded 225 mg (80.1%) of colorless crystals, m.p.: 69-75 °C (decomposition). –  $[\alpha]_{\text{D}}^{20} = -8.2$  ( $c = 4.92$ , CHCl<sub>3</sub>). – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 20 °C):  $\delta$  = 1.85-1.95 (m, 2 H, NCH<sub>2</sub>CH<sub>2</sub>), 2.22 (q,  $J = 7.3$  Hz, 2 H, NCHCCH<sub>2</sub>), 2.77 (dt,  $J = 9.8/8.8$  Hz, 1 H, NCH<sub>2</sub>), 2.93-3.01 (m, 1 H, OCH<sub>2</sub>CH<sub>2</sub>N), 3.27-3.36 (m, 2 H, OCH<sub>2</sub>CH<sub>2</sub>N), 3.39-3.47 (m, 1 H, OCH<sub>2</sub>CH<sub>2</sub>N), 3.54 (dt,  $J = 9.8/5.5$  Hz, 1 H, NCH<sub>2</sub>), 3.68-3.76 (m, 1 H, NCHC), 3.80 (s, 9 H, OCH<sub>3</sub>), 6.80-6.86 (m, 6 H, aromat. H), 7.28-7.33 (m, 6 H, aromat. H).

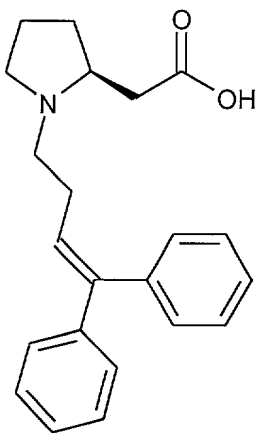
(e) (*R*)-*N*-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidine-2-carboxylic acid (**R-30c**)



**R-30c**

Saponification of methyl ester, General Procedure: 243 mg (0.48 mmol) of **R-27c** (see Example 1(e)), 80  $\mu$ l of 12 M NaOH, reaction time 4 h. Recrystallization from ether/*n*-pentane (1/1) afforded 186 mg (78.8%) of colorless crystals, m.p.: 69-75  $^{\circ}$ C (decomposition). The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-30c**  $[\alpha]_{\text{D}}^{20} = +8.1$  ( $c = 2.73$ ,  $\text{CHCl}_3$ ).

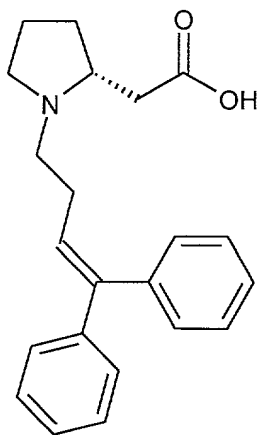
(f) (*S*)-[1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl]acetic acid (**S-31a**)



**S-31a**

Saponification of methyl ester, General Procedure: 139 mg (0.398 mmol) of **S-28a** (see Example 1(f)), 66  $\mu$ l of 12 M NaOH, reaction time 5 h. CC ( $\text{CH}_2\text{Cl}_2$ /ethanol = 8/2) afforded 110 mg (82.5%) of colorless crystals, m.p.: 130-137  $^\circ\text{C}$  (decomposition). –  $[\alpha]_{\text{D}}^{20} = -85.4$  ( $c = 1.30$ ,  $\text{CHCl}_3$ ). –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20  $^\circ\text{C}$ ):  $\delta = 1.67$ -1.94 (m, 3 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 2.05-2.15 (m, 1 H,  $\text{NCHCCH}_2$ ), 2.35 (td,  $J = 10.5/8.5$  Hz, 1 H,  $\text{NCH}_2$ ), 2.42-2.54 (m, 4 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ,  $\text{CH}_2\text{COO}$ ), 2.65 (dd,  $J = 17.1/5.1$  Hz, 1 H,  $\text{CH}_2\text{COO}$ ), 2.95-3.04 (m, 1 H,  $\text{NCHC}$ ), 3.06-3.16 (m, 1 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ), 3.19 (ddd,  $J = 10.5/7.1/3.9$  Hz, 1 H,  $\text{NCH}_2$ ), 6.02 (t,  $J = 7.3$  Hz, 1 H,  $=\text{CH}$ ), 7.14-7.44 (m, 10 H, aromat. H).

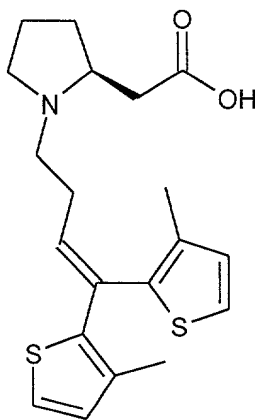
**(g) (R)-[1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl]acetic acid (R-31a)**



**R-31a**

Saponification of methyl ester, General Procedure: 136 mg (0.389 mmol) of **R-28a** (see Example 1(g)), 65  $\mu$ l of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 105 mg (80.4%) of colorless crystals, m.p.: 129-135  $^\circ\text{C}$  (decomposition). The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-31a**.  $[\alpha]_{\text{D}}^{20} = +86.5$  ( $c = 0.47$ ,  $\text{CHCl}_3$ ).

(h) (S)-{1-[4,4-Bis(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidin-2-yl}acetic acid (S-31b)

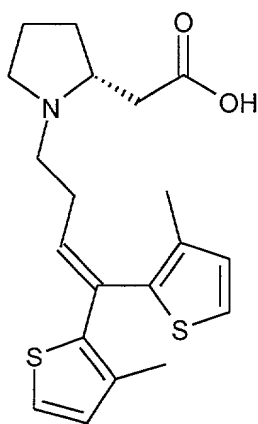


S-31b

Saponification of methyl ester, General Procedure: 85 mg (0.218 mmol) of **S-28b** (see Example 1(h)), 36  $\mu$ l of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 57 mg (69.6%) of a colorless oil.

$[\alpha]_D^{20} = -64.9$  ( $c = 0.85$ ,  $\text{CHCl}_3$ ). –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20  $^\circ\text{C}$ ):  $\delta = 1.66$ -1.79 (m, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 1.79-1.95 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 1.98 (s, 3 H,  $\text{CH}_3$ ), 2.03 (s, 3 H,  $\text{CH}_3$ ), 2.04-2.17 (m, 1 H,  $\text{NCHCCH}_2$ ), 2.38-2.55 (m, 5 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ,  $\text{CH}_2\text{COO}$ ,  $\text{NCH}_2$ ), 2.63 (dd,  $J = 16.9/5.3$  Hz, 1 H,  $\text{CH}_2\text{COO}$ ), 2.93-3.01 (m, 1 H,  $\text{NCHC}$ ), 3.03-3.12 (m, 1 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ), 3.29 (ddd,  $J = 11.0/7.5/4.0$  Hz, 1 H,  $\text{NCH}_2$ ), 6.01 (t,  $J = 7.3$  Hz, 1 H,  $=\text{CH}$ ), 6.76 (d,  $J = 5.1$  Hz, 1 H,  $\text{SC}=\text{CH}$ ), 6.87 (d,  $J = 5.1$  Hz, 1 H,  $\text{SC}=\text{CH}$ ), 7.06 (d,  $J = 5.1$  Hz, 1 H,  $\text{SCH}=\text{}$ ), 7.24 (d,  $J = 5.1$  Hz, 1 H,  $\text{SCH}=\text{}$ ).

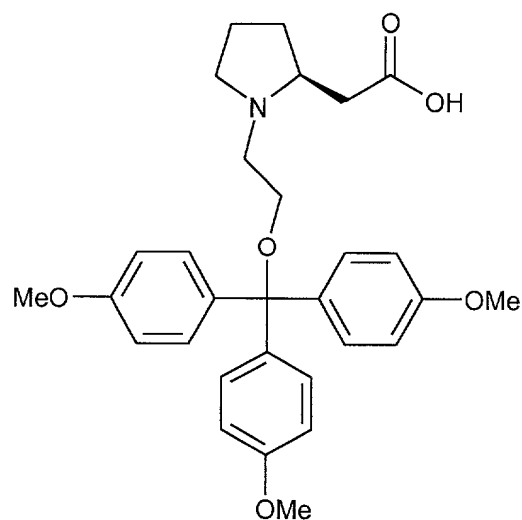
(i) (*R*)-{1-[4,4-Bis(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidin-2-yl}acetic acid  
(**R-31b**)



**R-31b**

Saponification of methyl ester, General Procedure: 105 mg (0.27 mmol) of **R-28b** (see Example 1(i)), 45  $\mu$ l of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 69 mg (68.1%) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-31b**.  $[\alpha]_D^{20} = +65.2$  ( $c = 1.02$ ,  $\text{CHCl}_3$ ).

(j) (*S*)-(1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl)acetic acid  
(**S-31c**)



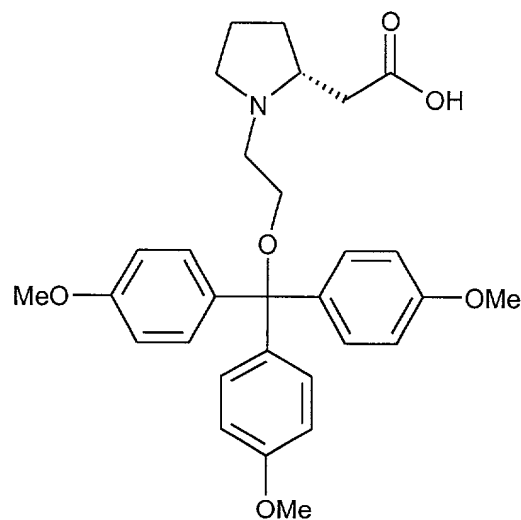
**S-31c**



Saponification of methyl ester, General Procedure: 220 mg (0.423 mmol) of **S-28c** (see Example 1(j)), 70  $\mu$ l of 12 M NaOH, reaction time 5 h. Recrystallization from ether/*n*-pentane (1/1) afforded 176 mg (82.2%) of colorless crystals, m.p.: 68-73 °C (decomposition).

$[\alpha]_D^{20} = -32.0$  ( $c = 0.66$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20 °C):  $\delta = 1.69$ -1.97 (m, 3 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 2.04-2.15 (m, 1 H,  $\text{NCHCCH}_2$ ), 2.44-2.59 (m, 3 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ,  $\text{NCH}_2$ ,  $\text{CH}_2\text{COO}$ ), 2.68 (dd,  $J = 17.2/4.3$  Hz, 1 H,  $\text{CH}_2\text{COO}$ ), 2.98-3.07 (m, 1 H,  $\text{NCHC}$ ), 3.07-3.17 (m, 1 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ), 3.26-3.44 (m, 3 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ,  $\text{NCH}_2$ ), 3.79 (s, 9 H,  $\text{OCH}_3$ ), 6.84-6.86 (m, 6 H, aromat. H), 7.28-7.34 (m, 6 H, aromat. H).

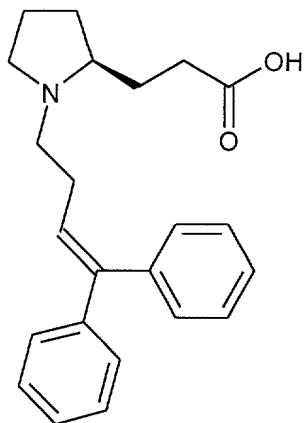
**(k) (*R*)-(1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl)acetic acid**  
**(R-31c)**



**R-31c**

Saponification of methyl ester, General Procedure: 135 mg (0.26 mmol) of **R-28c** (see Example 1(k)), 43  $\mu$ l of 12 M NaOH, reaction time 5 h. Recrystallization from ether/*n*-pentane (1/1) afforded 109 mg (83.0%) of colorless crystals, m.p.: 68-73 °C (decomposition). The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-31c**.  $[\alpha]_D^{20} = +32.7$  ( $c = 1.02$ ,  $\text{CHCl}_3$ ).

(l) 3-[(*S*)-1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl]propionic acid (**S-32a**)

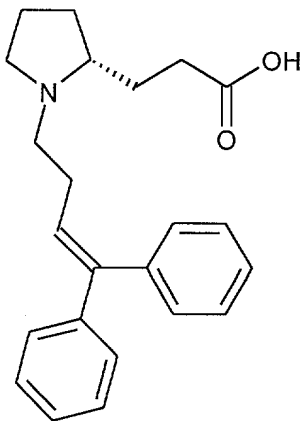


**S-32a**

Saponification of methyl ester, General Procedure: 122 mg (0.336 mmol) of **S-29a** (see Example 1(l)), 56  $\mu$ l of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 88 mg (75.0%) of a colorless oil.

$[\alpha]_D^{20} = -20.4$  ( $c = 1.10$ ,  $\text{CHCl}_3$ ). –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20 °C):  $\delta = 1.61$ -1.72 (m, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 1.72-1.90 (m, 4 H,  $\text{CH}_2\text{CH}_2\text{COO}$ ,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 1.90-2.02 (m, 1 H,  $\text{NCHCCH}_2$ ), 2.32-2.59 (m, 6 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ,  $\text{NCH}_2$ ,  $\text{CH}_2\text{COO}$ ), 2.85-2.94 (m, 1 H,  $\text{NCHC}$ ), 3.05 (td,  $J=11.0/5.0$  Hz, 1 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ), 3.18-3.25 (m, 1 H,  $\text{NCH}_2$ ), 6.03 (t,  $J=7.0$  Hz, 1 H,  $=\text{CH}$ ), 7.12-7.40 (m, 10 H, aromat. H).

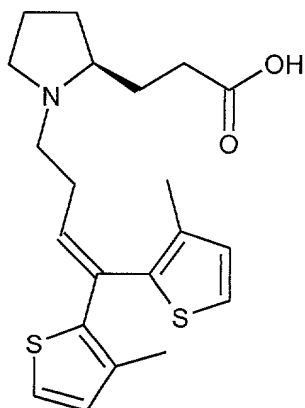
(m) 3-[(*R*)-1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl]propionic acid (**R-32a**)



**R-32a**

Saponification of methyl ester, General Procedure: 107 mg (0.336 mmol) of **R-29a** (see Example 1(m)), 49  $\mu$ l of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 76 mg (73.9%) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-32a**.  $[\alpha]_D^{20} = +19.5$  ( $c = 0.87$ ,  $\text{CHCl}_3$ ).

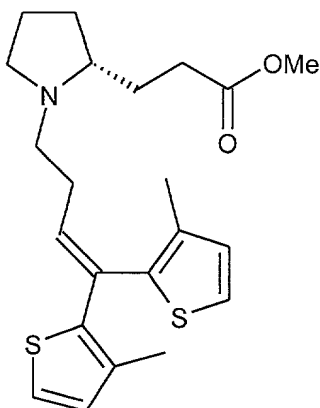
**(n) 3-[(*S*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]pyrrolidin-2-yl]propionic acid (**S-32b**)**



**S-32b**

Saponification of methyl ester, General Procedure: 100 mg (0.248 mmol) of **S-29b** (see Example 1(n)), 41  $\mu$ l of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 68 mg (70.5%) of a colorless oil.  $[\alpha]_D^{20} = -17.0$  ( $c = 0.73$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20  $^\circ\text{C}$ ):  $\delta = 1.70$ -1.85 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 1.85-2.10 (m, 4 H,  $\text{CH}_2\text{CH}_2\text{COO}$ ,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 1.96 (s, 3 H,  $\text{CH}_3$ ), 2.00 (s, 3 H,  $\text{CH}_3$ ), 2.40-2.75 (m, 5 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ,  $\text{NCH}_2$ ,  $\text{CH}_2\text{COO}$ ), 2.69 (td,  $J=11.3/5.0$  Hz, 1 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ), 3.03-3.15 (m, 2 H,  $=\text{CCH}_2\text{CH}_2\text{N}$ ,  $\text{NCHC}$ ), 3.28-3.38 (m, 1 H,  $\text{NCH}_2$ ), 5.96 (t,  $J = 7.3$  Hz, 1 H,  $=\text{CH}$ ), 6.74 (d,  $J = 4.4$  Hz, 1 H,  $\text{SC}=\text{CH}$ ), 6.85 (d,  $J = 4.4$  Hz, 1 H,  $\text{SC}=\text{CH}$ ), 7.05 (d,  $J = 4.4$  Hz, 1 H,  $\text{SCH}=\text{}$ ), 7.22 (d,  $J = 4.4$  Hz, 1 H,  $\text{SCH}=\text{}$ ).

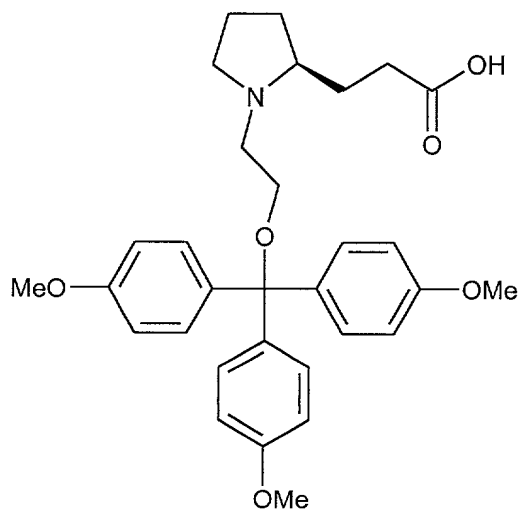
(o) 3-[(*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]pyrrolidin-2-yl]propionic acid  
(**R-32b**)



**R-32b**

Saponification of methyl ester, General Procedure: 170 mg (0.421 mmol) of **R-29b** (see Example 1(o)), 70  $\mu$ l of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 112 mg (68.3%) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-32b**.  $[\alpha]_D^{20} = +17.3$  ( $c = 0.91$ ,  $\text{CHCl}_3$ ).

(p) 3-[(*S*)-1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]propionic acid  
(**S-32c**)

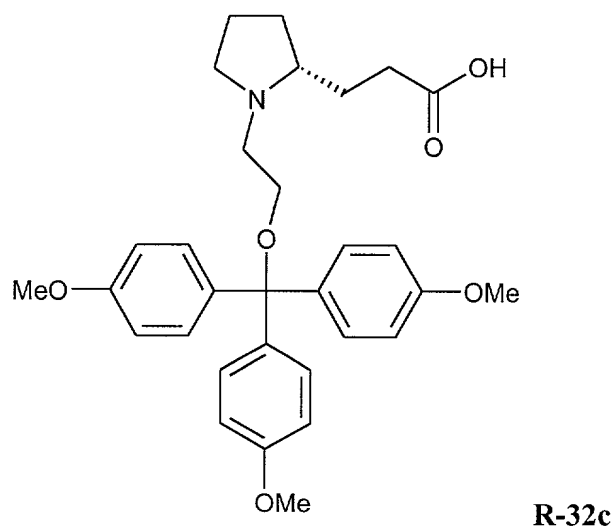


**S-32c**

Saponification of methyl ester, General Procedure: 93 mg (0.174 mmol) of **S-29c** (see Example 1(p)), 29  $\mu$ l of 12 M NaOH, reaction time 5 h. Recrystallization from ether/*n*-

pentane (1/1) afforded 73 mg (80.6%) colorless crystals, m.p.: 65-73 °C (decomposition).  $[\alpha]_D^{20} = -4.4$  ( $c = 0.51$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 20 °C):  $\delta = 1.73$ -2.07 (m, 6 H,  $\text{CH}_2\text{CH}_2\text{COO}$ ,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 2.36-2.46 (m, 1 H,  $\text{CH}_2\text{COO}$ ), 2.50-2.60 (m, 1 H,  $\text{CH}_2\text{COO}$ ), 2.72-3.81 (m, 2 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ,  $\text{NCH}_2$ ), 3.03-3.12 (m, 1 H,  $\text{NCHC}$ ), 3.18-3.28 (m, 1 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ), 3.40-3.50 (m, 1 H,  $\text{NCH}_2$ ), 3.49-3.61 (m, 2 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ), 3.70 (s, 9 H,  $\text{OCH}_3$ ), 6.78-6.86 (m, 6 H, aromat. H), 7.23-7.35 (m, 6 H, aromat. H).

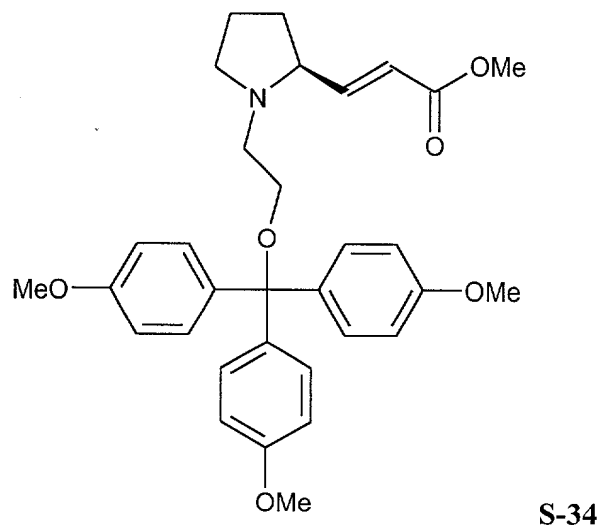
**(q) 3-[(R)-1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]propionic acid (R-32c)**



Saponification of methyl ester, General Procedure: 143 mg (0.268 mmol) of **R-29c** (see Example 1(q)), 45  $\mu\text{l}$  of 12 M NaOH, reaction time 5 h. Recrystallization from ether/*n*-pentane (1/1) afforded 115 mg (82.6%) of colorless crystals, m.p.: 64-72 °C (decomposition). The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-32c**.  $[\alpha]_D^{20} = +4.1$  ( $c = 0.50$ ,  $\text{CHCl}_3$ ).

### Example 3

(a) (*E*)-3-[(2*S*)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid methyl ester (S-34)

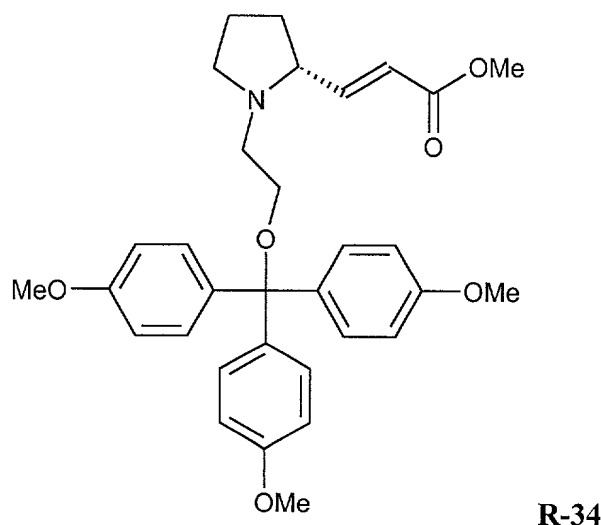


To a solution of 295 mg (0.584 mmol) of **S-27c** (see Example 1(d)) in 4 ml of toluene there was added dropwise at  $-60\text{ }^{\circ}\text{C}$  over a period of 10 min 1.4 ml (2.4 equiv.) of DIBAH solution (1 M in *n*-hexane), and the reaction mixture was stirred for 2 h at  $-60\text{ }^{\circ}\text{C}$ . Thereafter the reaction was stopped by dropwise addition of 0.5 ml of methanol, heated to RT and taken up in water and  $\text{Et}_2\text{O}$ . The aqueous phase was extracted three times with  $\text{Et}_2\text{O}$ , the combined organic phases were dried ( $\text{MgSO}_4$ ) and concentrated i. vac.. The oily residue (275 mg) was dissolved in 2.5 ml of acetonitrile and 30 mg (0.7 mmol, 1.2 equiv.) of LiCl and 123  $\mu\text{l}$  (0.7 mmol, 1.2 equiv.) of DIPEA were added thereto. Thereafter 113  $\mu\text{l}$  (0.7 mmol, 1.2 equiv.) of trimethylphosphono acetate was added dropwise. The reaction mixture was stirred for 16 h at RT, then concentrated i. vac., taken up in  $\text{Et}_2\text{O}$  and water, and the aqueous phase was extracted three times with  $\text{Et}_2\text{O}$ . The combined organic phases were dried ( $\text{MgSO}_4$ ) and concentrated i. vac.. Two CCs (*n*-hexane/ ether = 1/1) afforded 180 mg (58.0%) of a colorless oil.

$[\alpha]_{\text{D}}^{20} = -32.9$  ( $c = 0.99$ ,  $\text{CHCl}_3$ ). –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $20\text{ }^{\circ}\text{C}$ ):  $\delta = 1.53\text{--}1.66$  (m, 1 H,  $\text{NCHCCH}_2$ ),  $1.69\text{--}1.87$  (m, 2 H,  $\text{NCH}_2\text{CH}_2$ ),  $1.90\text{--}2.02$  (m, 1 H,  $\text{NCHCCH}_2$ ),  $2.25$  (q,  $J =$

8.6 Hz, 1 H, NCH<sub>2</sub>), 2.41 (dt,  $J = 12.9/5.8$  Hz, 1 H, OCH<sub>2</sub>CH<sub>2</sub>N), 2.86-3.02 (m, 2 H, OCH<sub>2</sub>CH<sub>2</sub>N, NCHC), 3.07-3.24 (m, 3 H, OCH<sub>2</sub>CH<sub>2</sub>N, NCH<sub>2</sub>), 3.74 (s, 3 H, COOCH<sub>3</sub>), 3.78 (s, 9 H, OCH<sub>3</sub>), 5.98 (d,  $J = 15.6$  Hz, 1 H, =CHCOO), 6.78-6.87 (m, 7 H, CH=, aromat. H), 7.31-7.37 (m, 6 H, aromat. H).

( b ) (*E*)-3-[(2*R*)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid methyl ester (**R-34**)

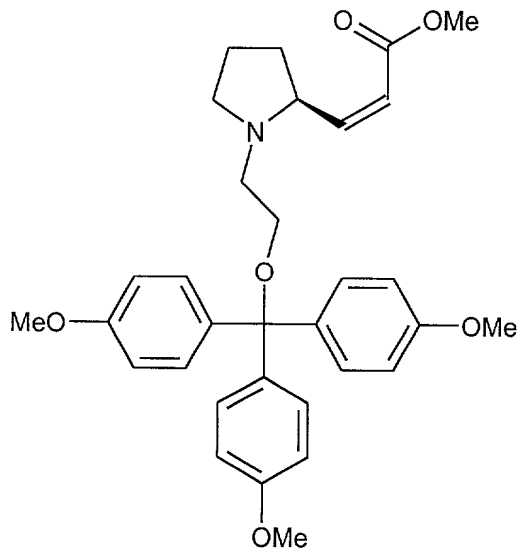


The synthesis of the compound was conducted according to the procedure for **S-34**.

Batch size: 308 mg (0.594 mmol) of **R-27c** (see Example 1(e)); 1.43 ml of DIBAH solution (1 M in *n*-hexane); 30 mg (0.7 mmol, 1.2 equiv.) of LiCl; 125  $\mu$ l (0.71 mmol, 1.2 equiv.) of DIPEA; 115  $\mu$ l (0.71 mmol, 1.2 equiv.) of trimethylphosphono acetate. Yield: 181 mg (59.5%); colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-34**.  $[\alpha]_{\text{D}}^{20} = +33.6$  ( $c = 1.0$ , CHCl<sub>3</sub>).

#### Example 4

(a) (Z)-3-[(2S)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid methyl ester (S-35)

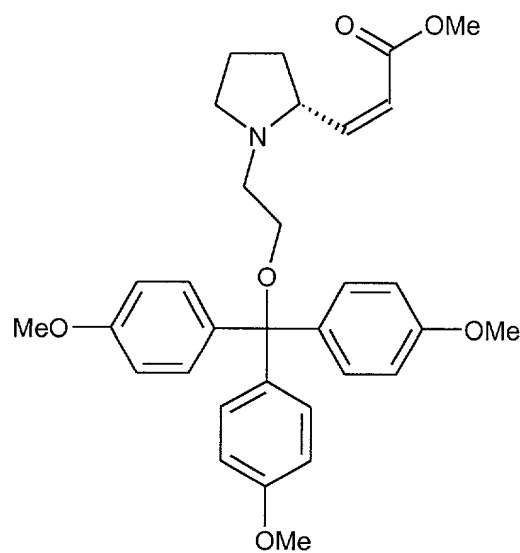


To a solution of 437 mg (0.865 mmol) of **S-27c** (see Example 1(d)) in 6 ml of toluene there was added dropwise at -60 °C and over a period of 10 min 2.1 ml (2.4 equiv.) DIBAH solution (1 M in *n*-hexane), and the reaction mixture was stirred for 2 h at -60 °C. Then the reaction was stopped by dropwise addition of 0.5 of methanol, heated to RT and taken up in water and Et<sub>2</sub>O. The aqueous phase was extracted three times with Et<sub>2</sub>O, the combined organic phases were dried (MgSO<sub>4</sub>) and concentrated i. vac.. The oily residue (410 mg) was dissolved in 5 ml of THF and added dropwise at -78 °C to a solution, prepared at -78 °C, of 1.143 g (5 equiv.) of crown ether (18-crown-6), 183 µl of (1 equiv.) of bis(3,3,3-trifluoroethoxy)phosphonic acid methyl ester and 1.15 ml (1 equiv.) of KN(TMS)<sub>2</sub> (15% solution in toluene) in 5 ml of THF. The reaction mixture was stirred for 1 h at RT, the reaction was stopped by addition of 1 ml of saturated NH<sub>4</sub>Cl solution, taken up in CH<sub>2</sub>Cl<sub>2</sub> and water, and the aqueous phase was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried (MgSO<sub>4</sub>) and concentrated i. vac.. Several CCs (*n*-hexane/ether = 1/1) afforded 197 mg (43.0%) of **S-35** as colorless oil. Additionally 66 mg (14.3%) of **S-34** could be isolated as colorless oil.



$[\alpha]_D^{20} = +9.6$  ( $c = 0.54$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $20^\circ\text{C}$ ):  $\delta = 1.42\text{--}1.55$  (m, 1 H,  $\text{NCHCCH}_2$ ),  $1.73\text{--}1.88$  (m, 2 H,  $\text{NCH}_2\text{CH}_2$ ),  $2.05\text{--}2.16$  (m, 1 H,  $\text{NCHCCH}_2$ ),  $2.25$  (q,  $J = 8.9$  Hz, 1 H,  $\text{NCH}_2$ ),  $2.49$  (dt,  $J = 12.6/6.3$  Hz, 1 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ),  $2.87$  (dt,  $J = 12.6/6.3$  Hz, 1 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ),  $3.10\text{--}3.24$  (m, 3 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ,  $\text{NCH}_2$ ),  $3.70$  (s, 3 H,  $\text{COOCH}_3$ ),  $3.78$  (s, 9 H,  $\text{OCH}_3$ ),  $4.01$  (q,  $J = 8.0$  Hz, 1 H,  $\text{NCHC}$ ),  $5.80$  (d,  $J = 11.6$  Hz, 1 H,  $=\text{CHCOO}$ ),  $6.18$  (dd,  $J = 11.6/8.0$  Hz, 1 H,  $\text{CH}=\text{}$ ),  $6.76\text{--}6.85$  (m, 6 H, aromat. H),  $7.29\text{--}7.38$  (m, 6 H, aromat. H).

**(b) (Z)-3-[(2R)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid methyl ester (R-35)**



**R-35**

The synthesis of the compound was conducted according to the procedure for **S-35**.

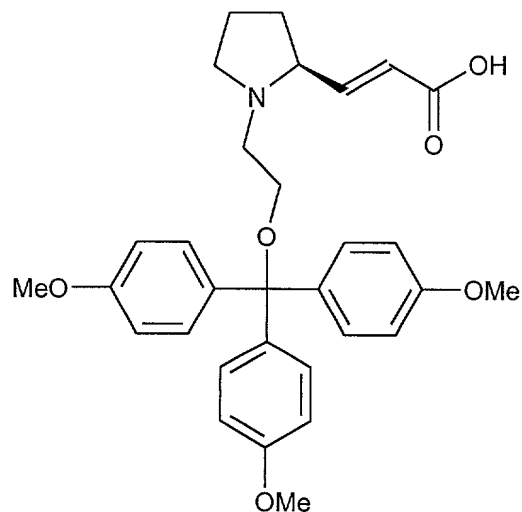
Batch size: 259 mg (0.513 mmol) of **R-27c** (see Example 1(e)); 1.23 ml of DIBAH solution (1 M in *n*-hexane); 678 mg (5 equiv.) of crown ether (18-crown-6), 108  $\mu\text{l}$  (1 equiv.) of bis(3,3,3-trifluoroethoxy)phosphonic acid methyl ester and 682  $\mu\text{l}$  (1 equiv.) of  $\text{KN}(\text{TMS})_2$  (15% solution in toluene).

Yield: 116 mg (42.2%) of **R-35** as colorless oil, as well as 39 mg (14.3%) of **R-34**. The analytical data of the compound is in agreement with those of the enantiomers.

$[\alpha]_D^{20} = -9.1$  ( $c = 0.50$ ,  $\text{CHCl}_3$ ).

## Example 5

(a) (*E*)-3-[(2*S*)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl] acrylic acid (**S-36**)

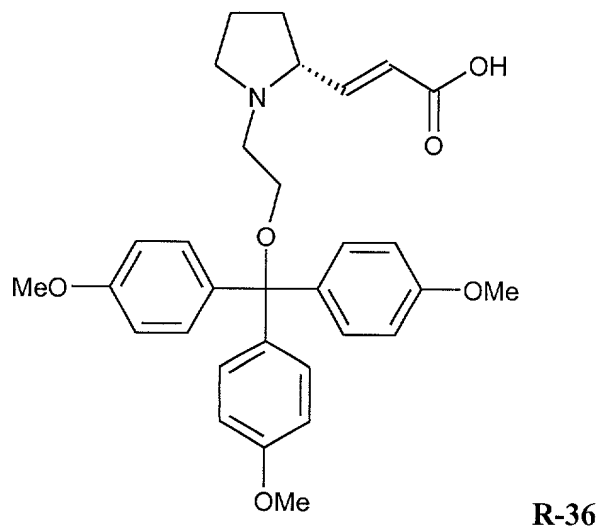


**S-36**

Saponification of methyl ester, general procedure: 157 mg (0.296 mmol) of **S-34** (see Example 3(a)), 49  $\mu$ l of 12 M NaOH, reaction time 5 h. Recrystallization from ether/*n*-pentane (1/1) afforded 120 mg (78.5%) of colorless crystals, m.p.: 78-86 °C (decomposition).

$[\alpha]_D^{20} = -15.6$  ( $c = 0.82$ ,  $\text{CHCl}_3$ ). –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20 °C):  $\delta = 1.67$ -1.80 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 1.85-1.98 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 2.49-2.59 (m, 2 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ,  $\text{NCH}_2$ ), 3.04-3.18 (m, 2 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ,  $\text{NCH}_2$ ), 3.23-3.37 (m, 2 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ), 3.60-3.68 (m, 1 H,  $\text{NCHC}$ ), 3.70 (s, 9 H,  $\text{OCH}_3$ ), 5.85 (d,  $J = 15.2$  Hz, 1 H,  $=\text{CHCOO}$ ), 6.67 (dd,  $J = 15.2/8.9$  Hz, 1 H,  $\text{CH}=\text{CHCOO}$ ), 6.71-6.76 (m, 6 H, aromat. H), 7.21-7.25 (m, 6 H, aromat. H).

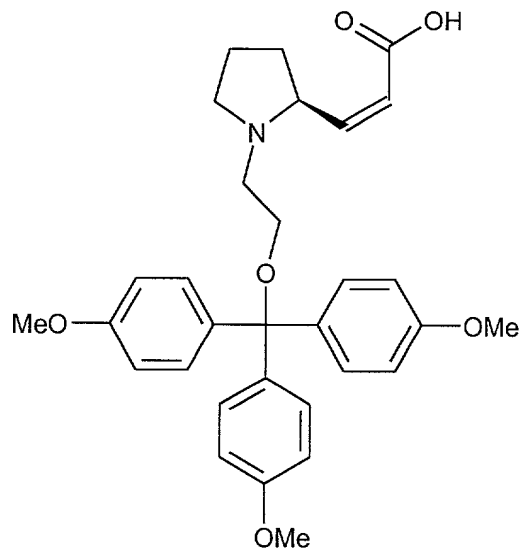
(b) (*E*)-3-[(2*R*)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid (**R-36**)



Saponification of methyl ester, General Procedure: 202 mg (0.38 mmol) of **R-34** (see Example 3(a)), 63  $\mu$ l of 12 M NaOH, reaction time 5 h. Recrystallization from ether/*n*-pentane (1/1) afforded 156 mg (79.3%); colorless crystals, m.p.: 78-86 °C (decomposition). The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-36**.  $[\alpha]_{\text{D}}^{20} = +16.2$  ( $c = 3.31$ ,  $\text{CHCl}_3$ ).

## Example 6

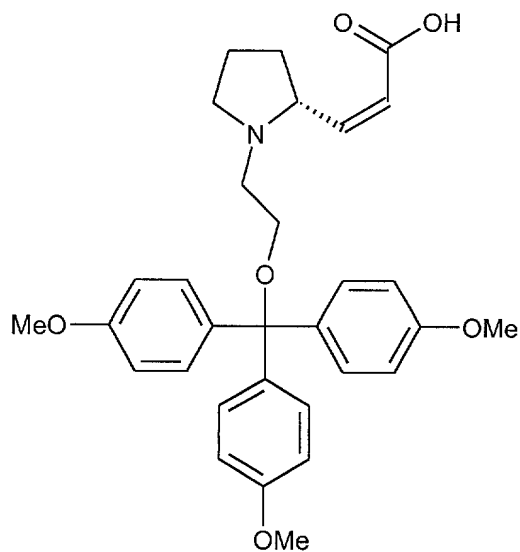
(a) (Z)-3-[(2S)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid (S-37)



Saponification of methyl ester, general procedure: 85 mg (0.16 mmol) of **S-35** (see Example 4(a)), 27  $\mu$ l of 12 M NaOH, reaction time 23 h. Recrystallization from ether/*n*-pentane (1/1) afforded 61 mg (73.7%); colorless crystals, m.p.: 100-105 °C (decomposition).

$[\alpha]_D^{20} = -12.7$  ( $c = 1.30$ ,  $\text{CHCl}_3$ ). –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 20 °C):  $\delta = 1.82$ -1.95 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 1.98-2.10 (m, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 2.18-2.27 (m, 1 H,  $\text{NCHCCH}_2$ ), 2.59-2.71 (m, 2 H,  $\text{NCH}_2$ ,  $\text{OCH}_2\text{CH}_2\text{N}$ ), 3.06 (dt,  $J = 13.2/5.5$  Hz, 1 H,  $\text{NCH}_2$ ), 3.39-3.50 (m, 4 H,  $\text{OCH}_2\text{CH}_2\text{N}$ ,  $\text{NCH}_2$ ,  $\text{NCHC}$ ), 3.79 (s, 9 H,  $\text{OCH}_3$ ), 5.99-6.09 (m, 2 H,  $\text{CH}=\text{CH}$ ), 6.78-6.85 (m, 6 H, aromat. H), 7.24-7.32 (m, 6 H, aromat. H).

(b) (Z)-3-[(2R)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid (**R-37**)

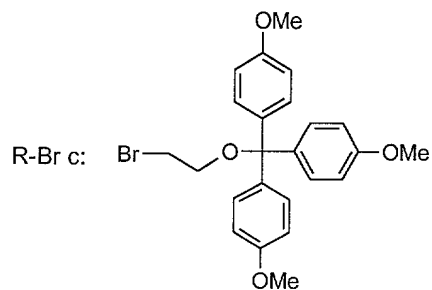
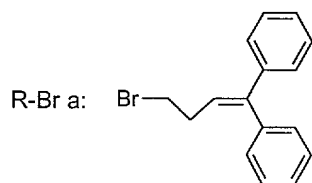
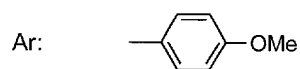
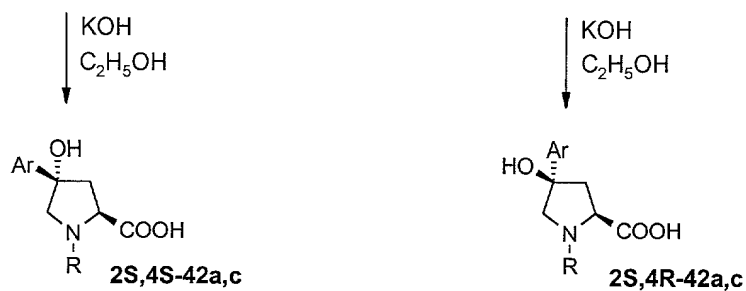
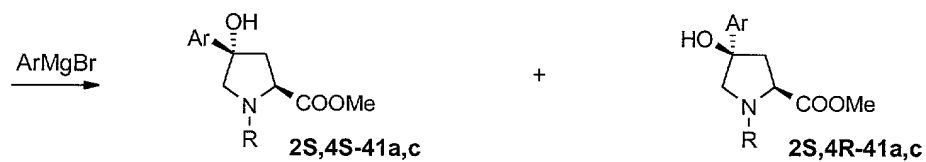
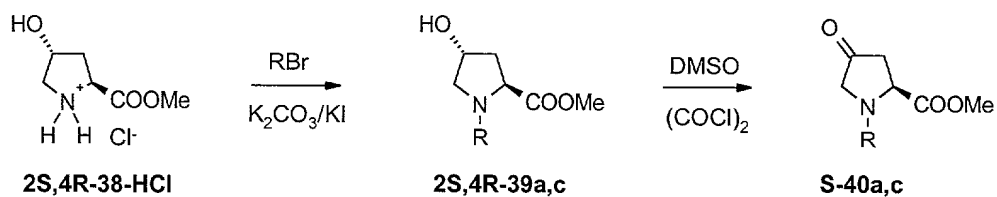


**R-37**

Saponification of methyl ester, general procedure: 91 mg (0.17 mmol) of **R-35** (see Example 4(b)), 29  $\mu$ l of 12 M NaOH, reaction time 23 h. Recrystallization from ether/*n*-pentane (1/1) afforded 65 mg (73.4%); colorless crystals, m.p.: 100-105 °C (decomposition). The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-37**.  $[\alpha]_{\text{D}}^{20} = +13.4$  ( $c = 1.57$ ,  $\text{CHCl}_3$ ).

Further compounds according to the present invention were prepared as illustrated in Reaction Scheme 9. The reactions are explained in more detail in the following working examples.

## Reaction Scheme 9

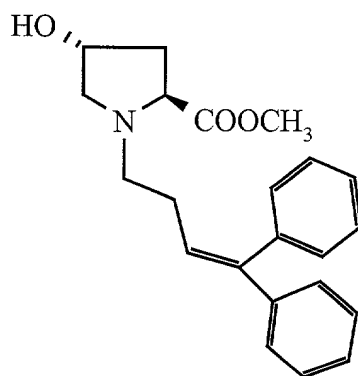


Synthesis by mirror like reaction  
 sequence in analogy to above  $\rightarrow$  **2R,4R-42a,c**  
**2R,4S-42a,c**

**(2*S*,4*R*)-4-Hydroxypyrrolidine-2-carboxylic acid methyl ester hydrochloride  
(2*S*,4*R*-38-HCl)**

Synthesis starting from 4.50 g (34.3 mmol) of (2*S*,4*R*) 4-hydroxypyrrolidine-2-carboxylic acid according to S.C. Mayer, J. Ramanjulu, M.D. Vera, A.J. Pfizenmayer, M.M. Joullie, *J. Org. Chem.* **1994**, 59, 5192-5205. Yield 5.50 g (96%). M.p.: 168-171°C (lit. 168-170°C),  $[\alpha]_D^{20} = -21.3^\circ$  (c = 1.0, CH<sub>3</sub>OH), (lit.  $-19.5^\circ$ , c = 1, CH<sub>3</sub>OH).

**(2*S*,4*R*)-N-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylic acid  
methyl ester (2*S*,4*R*-39a)**

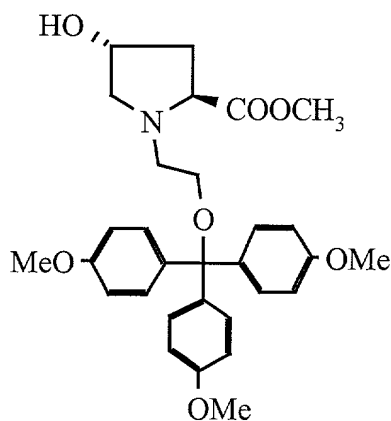


**2*S*,4*R*-39a**

50 mg (0.30 mmol) of potassium iodide and 454 mg (1.50 mmol) of 4,4-diphenylbut-3-en-1-yl bromide were added to a mixture of 274 mg (1.0 mmol) of **2*S*,4*R*-38-HCl** and 691 mg (5.0 mmol) of potassium carbonate in 8 ml of acetonitrile. The mixture was stirred at room temperature for 144 h. Inorganic salts were removed by filtration. The filtrate was concentrated, leaving a yellow oil. Purification by column chromatography (heptane/acetone = 4/1) afforded 277 mg (52 %) of a colorless oil.

$^1\text{H NMR}(\text{CDCl}_3)$ :  $\delta$  = 2.03 (ddd,  $J$  = 13.4/7.8/3.1 Hz, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 2.15-2.22 (m, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 2.30 (pseudo-q,  $J$  = 7.6 Hz, 2 H,  $=\text{CHCH}_2$ ), 2.41 (dd,  $J$  = 10.1/3.6 Hz, 1 H,  $\text{NCH}_2\text{CHO}$ ), 2.62 (dt,  $J$  = 12.2/7.5 Hz, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 2.82 (dt,  $J$  = 12.2/7.7 Hz, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 3.33 (dd,  $J$  = 10.1/5.5 Hz, 1 H,  $\text{NCH}_2\text{CHO}$ ), 3.53 (t,  $J$  = 7.7 Hz, 1 H,  $\text{NCHCOO}$ ), 3.67 (s, 3 H,  $\text{COOCH}_3$ ), 4.40-4.45 (m, 1 H,  $\text{CHOH}$ ), 6.07 (t,  $J$  = 7.3 Hz, 1 H,  $=\text{CHCH}_2$ ), 7.15-7.38 (m, 10 H, aromat. H).

**(2*S*,4*R*)-4-Hydroxy-N-{2-[tris(4-methoxyphenyl)methoxy]ethyl}-pyrrolidine-2- carboxylic acid methyl ester (2*S*,4*R*-39c)**



**2*S*,4*R*-39c**

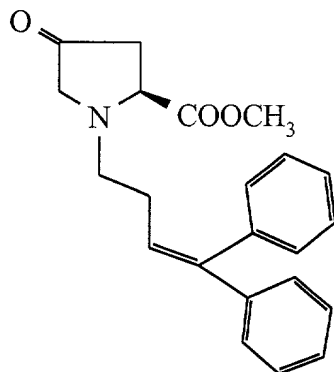
A mixture of 273 mg (1.49 mmol) of **(2*S*,4*R*-38-HCl)**, 682 mg (1.49 mmol) of 2-[[tris(methoxyphenyl)]methoxy]ethyl bromide, 680 mg (6.85 mmol) of potassium carbonate and 50 mg (0.3 mmol) of potassium iodide was stirred at room temperature for 9 days. Following filtration and concentration the crude product was purified by column chromatography (alumina, pH 7.5, mesh 70-230, heptane/acetone = 2/1), thereby obtaining 414 mg (53%) of a colorless oil.

$[\alpha]_{\text{D}}^{22} = -24.5^\circ$  ( $c$  = 0.55, ethanol). -  $^1\text{H NMR}(\text{CDCl}_3)$ :  $\delta$  = 2.00-2.07 (m, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 2.12-2.19 (m, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 2.57 (dd,  $J$  = 10.2/3.4 Hz, 1 H,  $\text{NCH}_2\text{CHO}$ ), 2.79-2.86 (m, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 2.91-2.98 (m, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 3. (20 (t,  $J$  =



6.1 Hz, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 3.38 dd,  $J = 10.2/5.4$  Hz, 1 H,  $\text{NCH}_2\text{CHO}$ ), 3.64-3.66 (m, 1 H,  $\text{NCHCOO}$ ), 3.65 (s, 3 H,  $\text{COOCH}_3$ ), 3.78 (s, 9 H,  $\text{Ar-OCH}_3$ ), 4.35-4.45 (m, 1 H,  $\text{CHOH}$ ), 6.83-6.79 (m, 6 H, 3'-H  $\text{Ar}_3\text{CO}$ ), 7.29-7.33 (m, 6 H, 2'-H  $\text{Ar}_3\text{CO}$ ).

**(2*S*)-N-(4,4-Diphenylbut-3-en-1-yl)-4-oxopyrrolidine-2- carboxylic acid methyl ester (S-40a)**

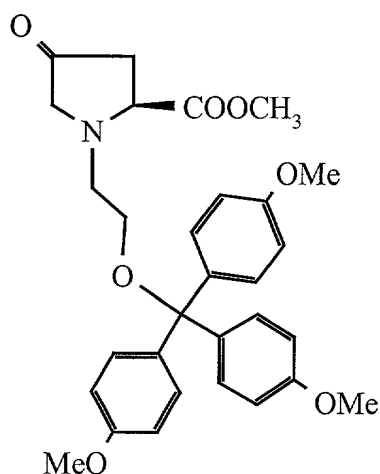


**S-40a**

193 mg (1.455 mmol) of oxalyl chloride was added to a solution of 227 mg (2.91 mmol) of DMSO in 4.5 ml of dichloromethane at  $-78^\circ\text{C}$  within 5 min. After 15 min, 357 mg (0.97 mmol) of **2S,4R-39a** in 1.5 ml of dichloromethane were added at  $-78^\circ\text{C}$ . Thereafter the reaction mixture was stirred for 30 min at  $-70$  -  $-60^\circ\text{C}$ . Following the addition of triethylamine (0.334 ml, 2.4 mmol) the temperature was held at  $-70$  -  $-60^\circ\text{C}$  for additional 15 min and then the mixture was slowly heated to room temperature and stirred for additional 15 min. The mixture was poured into a two-phase system consisting of 10 ml of dichloromethane, 15 ml of water and 3.7 ml of 0.85 M aqueous potassium hydroxide solution. The organic phase was washed with water, dried over sodium sulfate and concentrated, leaving an oil which upon purification by column chromatography (heptane/acetone = 4/1) afforded 312 mg (87%) of a colorless oil.  $[\alpha]_{\text{D}}^{25} = -32.4^\circ$  ( $c = 1.255$ , ethanol). -  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 2.26$  (pseudo-q,  $J = 7.3$  Hz, 2 H,  $=\text{CHCH}_2\text{CH}_2$ ), 2.43 (dd,  $J = 17.9/5.5$  Hz, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 2.54-2.62 (m, 2 H,  $\text{CH}_2\text{CHCOO}$  and  $\text{NCH}_2\text{CH}_2$ ), 2.77 (dt,  $J = 12/7$  Hz, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 2.91 (d,  $J = 17.2$  Hz, 1 H,  $\text{NCH}_2\text{CO}$ ),

3.29 (d,  $J = 17.2$  Hz, 1 H,  $\text{NCH}_2\text{CO}$ ), 3.65 (s, 3 H,  $\text{COOCH}_3$ ), 3.70 (dd,  $J = 7.8/5.5$  Hz, 1 H,  $\text{NCHCOO}$ ), 6.02 (t,  $J = 7.3$  Hz, 1 H,  $=\text{CHCH}_2\text{CH}_2$ ), 7.07-7.36 (m, 10 H, arom. H).

**(2*S*)-4-Oxo-N-{2-[tris(4-methoxyphenyl)methoxy]ethyl}-pyrrolidine-2-carboxylic acid methyl ester (S-40c)**



**S-40c**

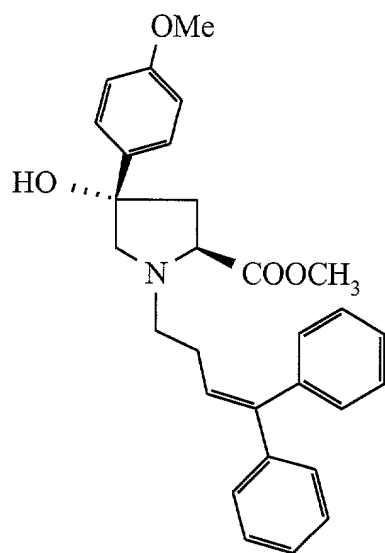
As described for **S-40a**, first 0.065 ml (0.921 mmol) of DMSO was reacted with 0.42 ml (0.461 mmol) of oxalyl chloride in dichloromethane and then there were added to the reaction mixture, at  $-70^\circ\text{C}$ , first 160 mg (0.307 mmol) of **2*S*,4*R*-39c** and after 10 min, triethylamine (0.143 ml, 0.993 mmol). Then slow heating to room temperature was effected, whereafter stirring was continued for 15 min. Subsequently 0.85 M aqueous potassium hydroxide solution was added until the aqueous phase was in the range of pH 7-8. Following extraction with dichloromethane, drying over sodium sulfate and concentration were effected. Upon purification by column chromatography (alumina pH 7.5, heptane/ethyl acetate = 3/1) 132 mg (83%) of a highly viscous, colorless oil was isolated.

$[\alpha]_D^{29} = -6.4^\circ$  ( $c = 1.83$ , ethyl acetate). -  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 2.48$  (dd,  $J = 18.0/5.5$  Hz, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 2.65 (dd,  $J = 18.0/7.8$  Hz, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 2.83 (dt,  $J = 13.0/5.6$  Hz, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 2.94 (dt,  $J = 5.6/13.0$  Hz, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 3.13 (d,  $J = 17.4$  Hz, 1 H,  $\text{NCH}_2\text{CO}$ ), 3.24 (t,  $J = 5.6$  Hz, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 3.44 (d,  $J = 17.4$  Hz, 1 H,

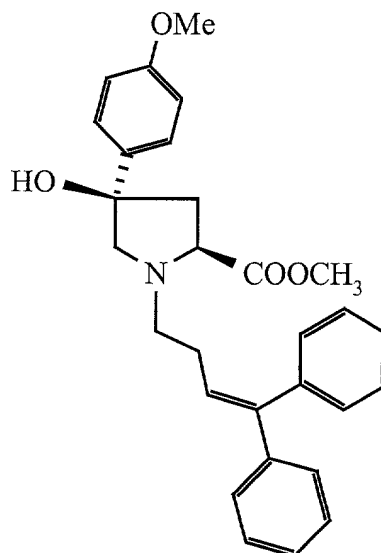
NCH<sub>2</sub>CO), 3.72 (s, 3 H, COOCH<sub>3</sub>), 3.78 (s, 9 H, ArOCH<sub>3</sub>), 3.84 (dd,  $J = 5.5/7.8$  Hz, 1 H, NCHCOO), 6.79-6.83 (m, 6 H, 3'-H Ar<sub>3</sub>CO), 7.29-7.32 (m, 6 H, 2'-H Ar<sub>3</sub>CO).

**(2*S*,4*S*) N-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2- carboxylic acid methyl ester (2*S*,4*S*-41a) and**

**(2*S*,4*R*) N-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2- carboxylic acid methyl ester (2*S*,4*R*-41a)**



**2*S*,4*S*-41a**



**2*S*,4*R*-41a**

#### Method A:

To 145 mg (0.415 mmol) of **S-40a** in 10 ml of ether there was added, at  $-75^{\circ}\text{C}$ , 1 ml of a 0.74 M solution of 4-methoxyphenylmagnesium bromide in ether. After 4 h at  $-75^{\circ}\text{C}$  the reaction was stopped by adding saturated ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with ether. The combined ethereal phases were dried over sodium sulfate and concentrated. Analysis by HPLC (column A see p.18, heptane/ethyl acetate = 70/30) of the mixture of diastereomers indicated a ratio of 96/4. Through purification by column chromatography (heptane/ethyl

acetate = 3/1) 104 mg (55 %) of the mixture of diastereomers and 13 mg of starting material **S-40a** were obtained.

#### Method B:

215 mg (0.875 mmol) of anhydrous cerium(III) chloride was dried in vacuo for 15 min at 140°C. Upon cooling to 0°C, 5 ml of a 0.76 M solution of 4-methoxyphenylmagnesium bromide (0.77 ml, 0.584 mmol) in THF was added. After stirring for one hour, the suspension was brought to -60°C and added to a solution of 120 mg (0.343 mmol) of **S-40a** in 3 ml of THF at -60°C. After 15 h the reaction was stopped at -60°C by adding saturated ammonium chloride solution. Analysis by HPLC (column A, heptane/ethyl acetate = 70/30) of the mixture of diastereomers indicated a ratio of 40/60. Upon purification by column chromatography (heptane/ethyl acetate = 3/1) 68 mg (43 %) of the mixture of diastereomers was obtained.

#### Method C:

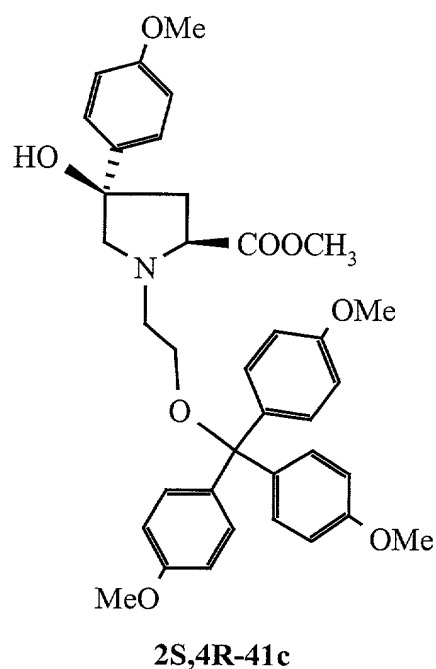
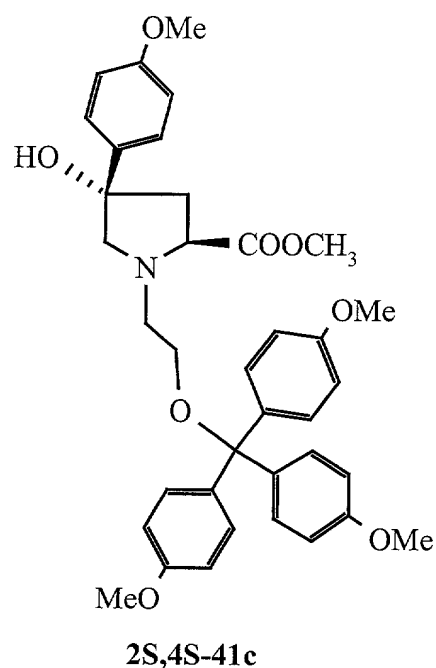
Conditions as for Method B, with the exception that the reaction was conducted at 0°C. Ratio of the diastereomers according to HPLC analysis (column A, heptane/ethyl acetate = 70/30) 48/52.

The predominant diastereomer could be prepared in pure form by recrystallization of the mixture of diastereomers obtained by Method A from diisopropyl ether. Colorless crystals, yield 72 mg (38 %), m.p.: 97-98°C.  $[\alpha]_D^{20} = -4.4^\circ\text{C}$  ( $c = 1.01$ ,  $\text{CHCl}_3$ ). -  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 2.26$  (pseudo-q,  $J = 7.5$  Hz, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 2.33 (d,  $J = 7.7$  Hz, 2 H,  $\text{CH}_2\text{CHCOO}$ ), 2.70 (dt,  $J = 12.0/7.7$  Hz, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 2.73 (d,  $J = 10.3$  Hz, 1 H,  $\text{NCH}_2\text{CO}$ ), 2.84 (dt,  $J = 12.0/7.7$  Hz, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 3.34 (d,  $J = 10.3$  Hz, 1 H,  $\text{NCH}_2\text{CO}$ ), 3.62 (s, 3 H,  $\text{Ar-OCH}_3$ ), 3.71 (s, 3 H,  $\text{COOCH}_3$ ), 3.77 (t,  $J = 7.7$  Hz, 1 H,  $\text{NCHCOO}$ ), 6.04 (t,  $J = 7.3$  Hz, 1 H,  $=\text{CHCH}_2\text{CH}_2$ ), 6.75-6.80 (m, 2 H, 3'-H  $\text{ArCOH}$ ), 7.08- 7.36 (m, 12 H, 2'-H of  $\text{ArCOH}$  and  $=\text{CPh}_2$ ).

The minor diastereomer could be isolated in pure form by recrystallization of the mixture

of diastereomers obtained by Method B from diisopropyl ether. Colorless crystals, m.p.: 94-96°C.  $[\alpha]_D^{20} = -49.4^\circ$  ( $c = 0.815$ ,  $\text{CHCl}_3$ ). -  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 2.15$  (ddd,  $J = 13.9/3.2/2.0$  Hz, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 2.25 (pseudo-q,  $J = 7.7/7.3$  Hz, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 2.49 (dd,  $J = 13.9/10.7$  Hz, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 2.63-2.70 (m, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 2.66 (d,  $J = 9.2$  Hz, 1 H,  $\text{NCH}_2\text{CO}$ ), 2.80 (dt,  $J = 7.7/12.1$  Hz, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 3.09 (dd,  $J = 9.2/1.9$  Hz, 1 H,  $\text{NCH}_2\text{CO}$ ), 3.44 (dd,  $J = 10.7/3.2$  Hz, 1 H,  $\text{NCHCOO}$ ), 3.66 (s, 3 H,  $\text{ArOCH}_3$ ), 3.72 (s, 3 H,  $\text{COOCH}_3$ ), 3.92 (s, 1 H, OH), 6.05 (t,  $J = 7.3$  Hz, 1 H,  $=\text{CHCH}_2$ ), 6.78-6.81 (m, 2 H, 3'-H  $\text{ArCOH}$ ), 7.09-7.33 (m, 12 H, 2'-H of  $\text{ArCOH}$ , and  $=\text{CPh}_2$ ).

**(2*S*,4*S*)-4-Hydroxy-4-(4-methoxyphenyl)-N-{2-[tris(4-methoxyphenyl)methoxy]ethyl}-pyrrolidine-2-carboxylic acid methyl ester (2*S*,4*S*-41c) and (2*S*,4*R*)-4-Hydroxy-4-(4-methoxyphenyl)-N-{2-[tris(4-methoxyphenyl)methoxy]ethyl}-pyrrolidine-2-carboxylic acid methyl ester (2*S*,4*R*-41c)**



### Method A:

To 251 mg (0.483 mmol) of **S-40c** in 20 ml of ether there was added, at  $-60^{\circ}\text{C}$ , 0.68 ml of a 0.833 M solution of 4-methoxyphenylmagnesium bromide in ether. After 20 h at  $-60^{\circ}\text{C}$  the reaction was stopped by saturated ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with ether. The combined ethereal phases were dried over sodium sulfate and concentrated. Analysis by HPLC (column A, heptane/ethyl acetate = 60 / 40) of the mixture of diastereomers indicated a ratio of 90/10. Upon purification by column chromatography (alumina, pH 7.5, heptane/acetone = 3/2) 104 mg (34 %) of the mixture of diastereomers and 98 mg of the starting material **S-40c** were obtained.

### Method B:

To 130 mg (0.527 mmol) of anhydrous cerium(III) chloride, dried in vacuo at  $130-140^{\circ}\text{C}$ , there were added, at  $0^{\circ}\text{C}$ , 5 ml of THF and 0.80 ml of a 0.67 M solution of 4-methoxyphenylmagnesium bromide (0.528 mol) in THF. After stirring for one hour, the suspension was cooled to  $-60^{\circ}\text{C}$  and added to a mixture of 196 mg (0.377 mmol) of **S-40c** in 6 ml of THF at  $-60^{\circ}\text{C}$ . After 19.5 h the reaction was stopped at  $-60^{\circ}\text{C}$  by adding saturated ammonium chloride solution. The organic phase was isolated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over magnesium sulfate and concentrated, leaving a yellow oil. Analysis by HPLC (column A, heptane/ethyl acetate = 60/40) of the mixture of diastereomers indicated a ration of 1/1. Upon purification by column chromatography (heptane/ethyl acetate = 3/2), 142 mg (60 %) of the mixture of diastereomers was obtained. The mixture of diastereomers was resolved by preparative HPLC (heptane/ethyl acetate = 55/45).

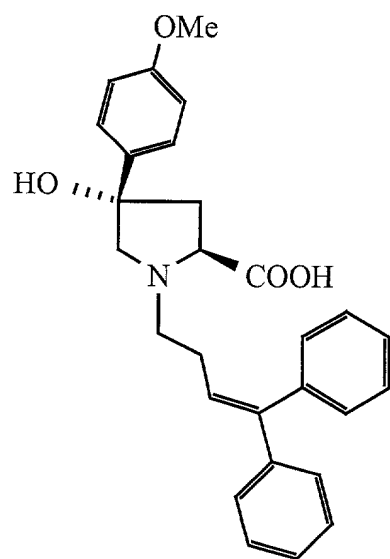
Predominant diastereomer: Yield: 57 mg (24%), highly viscous, colorless oil.  $[\alpha]_{\text{D}}^{20} = -7.1^{\circ}$  ( $c = 1.10$ , acetone).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta = 2.35-2.42$  (m, 2 H,  $\text{CH}_2\text{CHCOO}$ ), 2.54 (s, 1 H, OH), 2.96 (d,  $J = 10.7$  Hz, 1 H,  $\text{NCH}_2\text{CO}$ ), 2.92-3.00 (m, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 3.07 (dt,  $J = 12.9/5.9$  Hz, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 3.18-3.25 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 3.49 (d,  $J = 10.7$  Hz, 1 H,  $\text{NCH}_2\text{CO}$ ), 3.69 (s, 3 H,  $\text{ArOCH}_3$ ), 3.78 (s, 9 H,  $\text{ArOCH}_3$ ), 3.79 (s, 3 H,  $\text{COOCH}_3$ ), 3.94 (t,  $J = 6$  Hz, 1 H,  $\text{NCHCOO}$ ), 6.79-6.83 (m, 6 H,  $3'\text{-H Ar}_3\text{CO}$ ), 6.85-6.88

(m, 2 H, 3'-H *Ar*COH), 7.31-7.34 (m, 6 H, 2'-H *Ar*<sub>3</sub>CO), 7.38-7.42 (m, 2 H, 2'-H *Ar*COH).

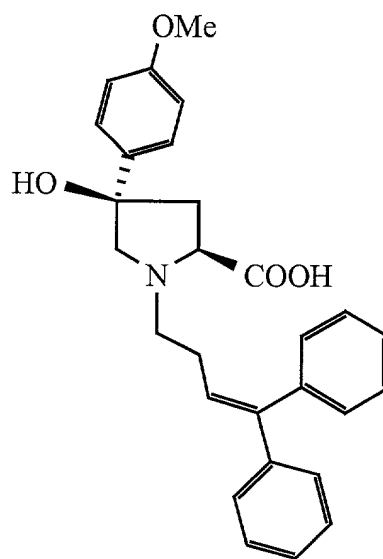
Minor diastereomer: Yield: 62 mg (26 %), highly viscous, colorless oil.

$[\alpha]_D^{20} = -18.6^\circ$  (c = 0.80, acetone). - <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 2.23 (ddd,  $J$  = 13.9/3/2 Hz, 1 H, CH<sub>2</sub>CHCOO), 2.56 (dd,  $J$  = 13.9/10.8 Hz, 1 H, CH<sub>2</sub>CHCOO), 2.89 (d,  $J$  = 9.2 Hz, 1 H, NCH<sub>2</sub>CO), 2.87-2.96 (m, 1 H, NCH<sub>2</sub>CH<sub>2</sub>), 2.98-3.05 (m, 1 H, NCH<sub>2</sub>CH<sub>2</sub>), 3.21 (dd,  $J$  = 9/2 Hz, 1 H, NCH<sub>2</sub>CO), 3.20-3.25 (m, 2 H, NCH<sub>2</sub>CH<sub>2</sub>O), 3.63 (dd,  $J$  = 10.8/3.2 Hz, 1 H, NCHCOO), 3.71 (s, 3 H, COOCH<sub>3</sub>), 3.79 (s, 9 H, ArOCH<sub>3</sub>), 3.81 (s, 3 H, ArOCH<sub>3</sub>), 6.81-6.84 (m, 6 H, 3'-H Ar<sub>3</sub>CO), 6.86-6.90 (m, 2 H, 3'-H *Ar*COH), 7.31-7.35 (m, 6 H, 2'-H Ar<sub>3</sub>CO), 7.37-7.40 (m, 2 H, 2'-H *Ar*COH).

(2*S*,4*S*)-*N*-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2- carboxylic acid (2*S*,4*S*-42a) and  
 (2*S*,4*R*)-*N*-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2- carboxylic acid (2*S*,4*R*-42a)



2*S*,4*S*-42a



2*S*,4*R*-42a

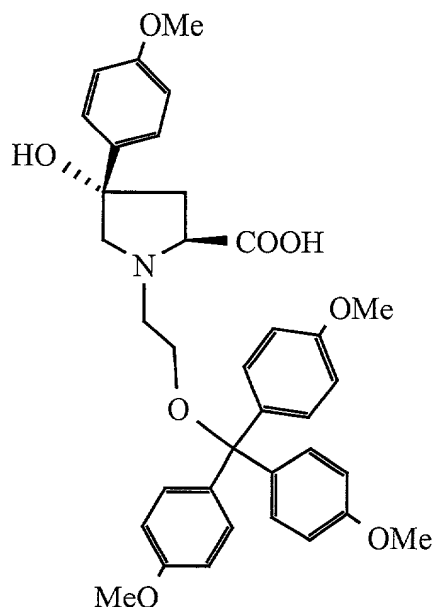
Following the addition of 0.386 ml of 0.85 M aqueous potassium hydroxide solution, 50 mg (0.109 mmol) of the predominant diastereomer of 2*S*,4*S*-41a/2*S*,4*R*-41a (Method A) in 1.7 ml of ethanol was stirred for one hour at room temperature. Subsequently 0.3 ml of 1 M hydrochloric acid was added to adjust the pH to 6-7 and 1.0 ml of 0.2 M phosphate buffer (pH 6.6) was added to the mixture. Thereafter careful concentration in vacuo ( $T < 30^{\circ}\text{C}$ ) was carried out. The residue was additioned with water and filtered. The solid obtained upon filtration was dried in air and subsequently purified by column chromatography (diisopropyl ether  $\rightarrow$  ethanol gradient). This afforded 36 mg (74%) of colorless crystals, m.p.: 173-175°C.  $[\alpha]_{\text{D}}^{20} = -28.0^{\circ}$  ( $c = 0.64$ , methanol). –  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta = 2.42$  (dd,  $J = 13.3/12.1$  Hz, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 2.57 (pseudo-q,  $J = 7.6$



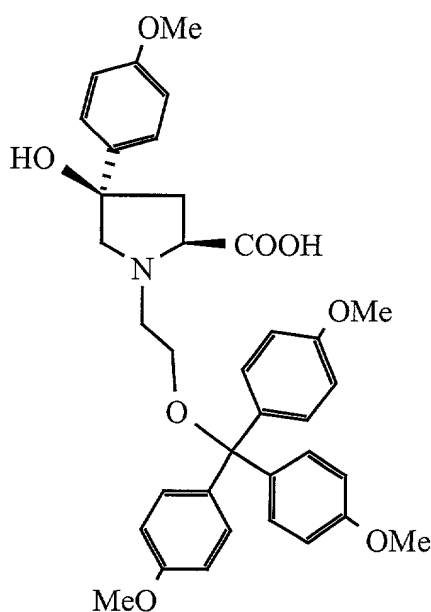
Hz, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 2.65 (ddd,  $J = 13.3/6.7/2.1$  Hz, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 3.26-3.33 (m, 1 H,  $\text{NCH}_2\text{CO}$ ), 3.33-3.40 (m, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 3.54 (dt,  $J = 12.3/8.0$  Hz, 1 H,  $\text{NCH}_2\text{CH}_2$ ), 3.68 (d,  $J = 12.3$  Hz, 1 H,  $\text{NCH}_2\text{CO}$ ), 3.78 (s, 3 H,  $\text{ArOCH}_3$ ), 4.25 (dd,  $J = 12.1/6.7$  Hz, 1 H,  $\text{NCHCOO}$ ), 6.12 (t,  $J = 7.4$  Hz, 1 H,  $=\text{CHCH}_2$ ), 6.90-6.93 (m, 2 H, 3'-H  $\text{ArCOH}$ ), 7.17-7.44 (m, 12 H, 2'-H  $\text{ArCOH}$  and  $=\text{CPh}_2$ ).

Following the addition of 0.154 ml of a 0.85 M aqueous solution of potassium hydroxide, 20 mg (0.0437 mmol) of the minor diastereomer of **2S,4S-41a/2S,4R-41a (Method A)** in 0.6 ml of ethanol was stirred at room temperature for 1 h. Thereafter the pH was adjusted to 6-7 with 1 M hydrochloric acid, and 0.6 ml of 0.2 M phosphate buffer (pH 5.5) was added to the mixture. Thereafter careful concentration in vacuo was carried out ( $T < 30^\circ\text{C}$ ). The residue was purified by column chromatography (diisopropyl ether  $\rightarrow$  ethanol gradient) and afforded 17 mg (88 %) as yellowish crystals, m.p.:  $168\text{--}173^\circ\text{C}$ .  $[\alpha]_{\text{D}}^{20} = -35.7^\circ$  ( $c = 0.585$ ,  $\text{CHCl}_3$ ). -  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta = 2.53$  (d,  $J = 13.5$  Hz, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 2.57-2.65 (m, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 2.85 (dd,  $J = 13.5/11.4$ , 1 H,  $\text{CH}_2\text{CHCOO}$ ), 3.25 (d,  $J = 11.0$  Hz, 1 H,  $\text{NCH}_2\text{CO}$ ), 3.25-3.35, 3.42-3.46 (m, 3 H,  $\text{NCH}_2\text{CO}$  and  $\text{NCH}_2\text{CH}_2$ ), 3.78 (s, 3 H,  $\text{ArOCH}_3$ ), 4.00-4.02 (m, 1 H,  $\text{NCHCOO}$ ), 6.11 (dd, 1 H,  $J = 6.6/8.4$  Hz,  $\text{CH}_2\text{CH}_2\text{CH=}$ ), 6.89-6.92 (m, 2 H, 3'-H  $\text{ArCOH}$ ), 7.23-7.42 (m, 12 H, 2'-H  $\text{ArCOH}$  and  $=\text{CPh}_2$ )

(2*S*,4*S*)-4-Hydroxy-4-(4-methoxyphenyl)-N-{2-[tris(4-methoxyphenyl)methoxy]ethyl}-pyrrolidine-2-carboxylic acid (**2S,4S-42c**) and (2*S*,4*R*)-4-Hydroxy-4-(4-methoxyphenyl)-N-{2-[tris(4-methoxyphenyl)methoxy]ethyl}-pyrrolidine-2-carboxylic acid (**2S,4R-42c**)



**2S,4S-42c**



**2S,4R-42c**

Following the addition of 0.39 ml of a 0.85 M aqueous solution of potassium hydroxide, 30 mg (0.0988 mmol) of the predominant diastereomer of **2S,4S-41c/2S,4R-41c** (**Method A**) in 1.0 ml of ethanol was stirred at room temperature for 105 min. Subsequently the pH was adjusted to 7-8 with 0.35 ml of 1 M hydrochloric acid, and 1.0 ml of 0.2 M phosphate buffer (pH 6.6) was added to the mixture. Thereafter careful concentration in vacuo was carried out ( $T < 25^{\circ}\text{C}$ ). The residue was washed with water and dried in vacuo. Yield: 26 mg (89%); colorless crystals, m.p.: 138-139°C.

$[\alpha]_{\text{D}}^{20} = -3.9^{\circ}$  ( $c = 0.85$ , methanol). -  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta = 2.32$  (dd,  $J = 13.3/11.6$  Hz, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 2.57 (ddd,  $J = 13.3/7.1/2.1$  Hz, 1 H,  $\text{CH}_2\text{CHCOO}$ ), 3.14 (dd,  $J = 12.5/2.1$  Hz, 1 H,  $\text{NCH}_2\text{CO}$ ), 3.32-3.41 (m, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 3.37 (d,  $J = 12.5$  Hz, 1 H,  $\text{NCH}_2\text{CO}$ ), 3.44-3.54 (m, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 3.63 (s, 9 H,  $\text{ArOCH}_3$ ), 3.70 (s, 3 H,

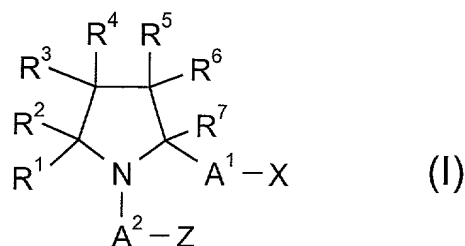
ArOCH<sub>3</sub>), 4.29 (dd,  $J = 11.6/7.1$  Hz, 1 H, NCHCOO), 6.73-6.76 (m, 6 H, 3'-H *Ar*<sub>3</sub>CO), 6.78-6.81 (m, 2 H, 3'-H ArCOH), 7.23-7.26 (m, 8 H, 2'-H ArCOH and *Ar*<sub>3</sub>CO).

Following the addition of 0.465 ml of a 0.85 M aqueous potassium hydroxide solution, 62 mg (0.0988 mmol) of the minor diastereomer of **2S,4S-41c/2S,4R-41c (Method A)** in 2.0 ml of ethanol was stirred at room temperature for 3.5 h. Subsequently the pH was adjusted to 7-8 with 0.35 ml of 1 M hydrochloric acid, and 2.0 ml of 0.2 M phosphate buffer (pH 6.6) was added to the mixture. Thereafter careful concentration in vacuo was carried out ( $T < 25^{\circ}\text{C}$ ). The residue was washed with water and dried in vacuo. This afforded 54 mg (89 %) of colorless crystals, m.p.: 105-108°C.

$[\alpha]_{\text{D}}^{20} = +1.5^{\circ}$  ( $c = 1.15$ , methanol). - <sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta = 2.46$ -2.50 (d, broadened,  $J = 13.5$  Hz, 1 H, CH<sub>2</sub>CHCOO), 2.75 (dd,  $J = 13.5/11.5$ , 1 H, CH<sub>2</sub>CHCOO), 3.05-3.14 (m, 2 H, NCH<sub>2</sub>CO), 3.25-3.32 (m, 2 H, NCH<sub>2</sub>CH<sub>2</sub>), 3.49-3.62 (m, 2 H, NCH<sub>2</sub>CH<sub>2</sub>), 3.67 (s, 9 H, ArOCH<sub>3</sub>), 3.70 (s, 3 H, ArOCH<sub>3</sub>), 4.06 (dd,  $J = 11.5/2$  Hz, 1 H, NCHCOO), 6.77-6.84 (m, 8 H, 3'-H ArCOH and *Ar*<sub>3</sub>CO), 7.22-7.25 (m, 2 H, 2'-H ArCOH), 7.28-7.32 (m, 6 H, 2'-H *Ar*<sub>3</sub>CO).

## Claims

### 1. Compounds of general formula (I)



wherein

$R^1$  to  $R^7$  are independently selected from H, optionally substituted  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl, optionally substituted aryl or heteroaryl, OH, halogen, CN,  $OR^{12}$ ,  $SR^{12}$ ,  $COR^{12}$ ,  $COOR^{12}$ ,  $SOR^{12}$ ,  $SO_2R^{12}$ ,  $NR^{13}R^{14}$ ,  $CONR^{13}R^{14}$ ,  $SO_2NR^{13}R^{14}$ , where  $R^{13}$  and  $R^{14}$  are independently selected from H and  $C_{1-3}$  alkyl and  $R^{12}$  represents  $C_{1-6}$  alkyl ; two of  $R^1$  to  $R^7$  each may be combined to form a 3- to 6-membered ring system, which ring system may contain one or more heteroatoms;  $R^1$  and  $R^2$  and/or  $R^3$  and  $R^4$  and/or  $R^5$  and  $R^6$  may be replaced by an optionally substituted alkylidene group or =O; and two of  $R^1$  to  $R^7$  which are positioned at adjacent carbon atoms may each be replaced by a C-C bond;

$A^1$  represents  $(-CR^8R^9)_n$ , optionally substituted  $C_{3-6}$  cycloalkylene or a combination of these groups,  $R^8$  and  $R^9$  being independently selected from H,  $C_{1-6}$  alkyl, halogen, OH,  $OR^{12}$  and  $NR^{13}R^{14}$  and where for  $n \geq 2$   $R^8$  and  $R^9$  may be different in each group and two groups selected from  $R^8$  and  $R^9$  at adjacent C atoms may be replaced by a C-C bond, and a group -O- or -CO- may be positioned between two adjacent groups  $CR^8R^9$  ; and wherein one of  $R^8$  and  $R^9$  may be combined with one of  $R^1$  to  $R^7$  to form a 5- to 7-membered ring structure; and  $n = 0, 1, 2, 3$  or  $4$ ;

X is COOM or a group which can be converted into COOM under physiological conditions, M representing H or a pharmaceutically acceptable cation;

$A^2$  is  $(-CR^{10}R^{11}-)_m$ , where  $R^{10}$  and  $R^{11}$  are independently selected from H,  $C_{1-2}$  alkyl and halogen; where for  $m \geq 2$  the groups  $R^{10}$  and  $R^{11}$  may be different in each group, a group -O- or -S- may be positioned between two adjacent groups, and two groups selected from  $R^{10}$  and  $R^{11}$  at adjacent C atoms may be replaced by a C-C bond; and wherein one of  $R^{10}$  and  $R^{11}$  may be combined with one of  $R^1$  to  $R^9$  to form a 5- to 7-membered ring structure; and m is 1, 2, 3, or 4;

Z is selected from  $Y_3CO$ ,  $Y_2C=CR^{15}$  and  $Y_2C=N-O$ , where  $R^{15}$  is H,  $C_{1-3}$  alkyl or halogen and the groups Y independently are optionally substituted  $C_{6-12}$  aryl or optionally substituted  $C_{2-5}$  heteroaryl having up to three heteroatoms selected from N, O and S, and the groups Y may be linked by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from -O-, -S-, -NH-, -O-, -CH=CH-, -CH=N-, -CH<sub>2</sub>- and -CH<sub>2</sub>CH<sub>2</sub>-;

as well as the individual stereoisomers of these compounds.

2. Compounds according to claim 1, wherein  $R^7$  is hydrogen and  $R^1$  to  $R^6$  are independently selected from optionally substituted  $C_{1-3}$  alkyl, halogen, OH, CN, optionally substituted phenyl and optionally substituted heteroaryl having 5 to 10 ring members and one or two heteroatoms selected from O, N and S, and in particular from hydrogen,  $C_{1-3}$  alkyl and phenyl.

3. Compounds according to any one of claims 1 and 2, wherein all of  $R^1$  to  $R^7$  represent hydrogen.

4. Compounds according to any one of claims 1 to 3, wherein  $A^1$  is  $(-CR^8R^9-)_n$ ,  $R^8$  and  $R^9$  being independently selected from H and  $C_{1-3}$  alkyl and being particularly hydrogen and n having a value of 0, 1 or 2, in particular of 1 or 2.

5. Compounds according to any one of claims 1 to 4, wherein X is COOM, with M = H, Na, K, NH<sub>4</sub>, Ca<sub>0.5</sub> or Mg<sub>0.5</sub>, and preferably H or Na.

6. Compounds according to any one of claims 1 to 5, wherein  $R^{10}$  and  $R^{11}$  are independently selected from H and  $C_{1-2}$  alkyl, and preferably are both H, and m is 2 or 3, in particular 2.

7. Compounds according to any one of claims 1 to 6, wherein Z is  $Y_2CO$  and the groups Y, which preferably are the same, are phenyl which optionally is substituted with one or two substituents, the substituents being selected from  $C_{1-3}$  alkoxy,  $C_{1-3}$  alkyl, halogen, OH,  $NO_2$ , CN and  $NR^{13}R^{14}$  and  $R^{13}$  and  $R^{14}$  are defined as in claim 1.

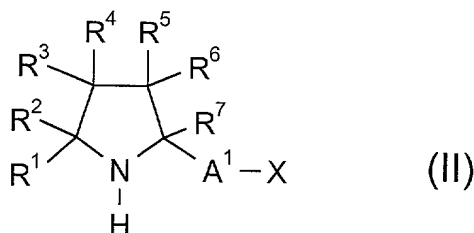
8. Compounds according to claim 7, wherein the phenyl radicals are mono- or disubstituted and the substituents are preferably selected from  $C_{1-2}$  alkoxy, in particular methoxy, and  $C_{1-2}$  alkyl, in particular methyl.

9. Compounds according to any one of claims 1 to 6, wherein Z is  $Y_2C=CR^{15}$  or  $Y_2C=N-O$ , the groups Y being preferably the same and representing optionally substituted phenyl or optionally substituted heteroaryl having 5 or 6 ring members and one or two heteroatoms selected from O, N and S and  $R^{15}$  is H or  $CH_3$ , preferably H.

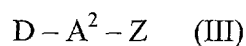
10. Compounds according to claim 9, wherein the radicals Y carry 0, 1 or 2 substituents, the substituents being selected from  $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy, halogen, OH,  $NO_2$ , CN and  $NR^{13}R^{14}$ , as defined in claim 1.

11. Compounds according to any one of claims 1 – 10, wherein the substituents Y are the same and are selected from phenyl, 4-methoxyphenyl and 3-methyl-2-thienyl.

12. Process for the preparation of a compound of general formula (I), according to claim 1, wherein a compound of general formula (II)



wherein  $R^1$  to  $R^7$ ,  $A^1$  and  $X$  are as defined in claim 1 is reacted with a compound of the general formula (III):



wherein  $A^2$  and  $Z$  are defined as in claim 1 and  $D$  represents a group which can react with the group  $N-H$  of the compound of general formula (II) to form  $HD$ , in particular halogen.

13. Pharmaceutical composition, comprising at least one pharmaceutically acceptable carrier or excipient and at least one compound of general formula (I) as defined in any one of claims 1 to 11.

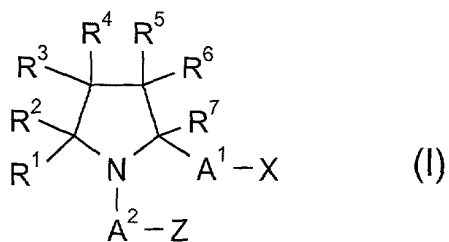
14. Compounds according to any one of claims 1 to 11 for use in a method for the treatment of the human or animal body.

15. Use of the compounds according to any one of claims 1 to 11 for the manufacture of a medicament for the treatment of diseases which can be ameliorated or cured by an amplification of the GABAergic neurotransmission.

## Abstract

### GABA Uptake Inhibitors Having a Pyrrolidine Structure

The invention relates to compounds of general formula (I)



wherein  $R^1$  to  $R^7$ ,  $A^1$ ,  $A^2$ ,  $X$  and  $Z$  are defined as in Claim No. 1. These compounds are suited as GABA uptake inhibitors for treating diseases such as epilepsy.



# Declaration and Power of Attorney For Utility or Design Patent Application

Erklärung für Patentanmeldungen zur Gebrauchseignung und Entwicklung  
mit Vollmacht

## German Language Declaration

Als nachstehend benannter Erfinder erkläre ich hiermit an Eides  
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angehörigkeit den im nachstehenden nach meinem Namen  
aufgeführten Angaben entsprechen, daß ich nach bestem Wissen der  
ursprüngliche, erste und alleinige Erfinder (falls nachstehend nur ein  
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Gegenstandes bin, für den dieser Antrag gestellt wird und für den  
ein Patent für die Erfindung mit folgendem Titel beantragt wird:

GABA-UPTAKE-INHIBITOREN MIT  
PYRROLIDINSTRUKTUR

deren Beschreibung hier beigelegt ist, es sei denn (in diesem Falle  
Zutreffendes bitte ankreuzen), diese Erfindung

☒ wurde angemeldet am 3. September 1999  
unter der US-Anmeldenummer \_\_\_\_\_  
und wurde am \_\_\_\_\_ abgeändert (falls zutreffend)  
oder  
☐ unter der PCT internationalen Anmeldungsnummer \_\_\_\_\_  
PCT/EP99/06486  
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Anmeldungen angegeben, deren Anmeldetag dem der Anmeldung,  
für welche Priorität beansprucht wird, vorangeht.

Prior Foreign Applications  
Frühere ausländische Anmeldungen

<u>198 40 611.8</u>	<u>Germany</u>
(Number)	(Country)
(Nummer)	(Land)
_____	_____
(Number)	(Country)
(Nummer)	(Land)

<u>5. September 1998</u>
(Day/Month/Year Filed)
(Tag/Monat/Jahr der Anmeldung)
_____
(Day/Month/Year Filed)
(Tag/Monat/Jahr der Anmeldung)

Priority Claimed  
Prioritätsanspruch

<input checked="" type="checkbox"/>	<input type="checkbox"/>
Yes	No
Ja	Nein
<input type="checkbox"/>	<input type="checkbox"/>
Yes	No
Ja	Nein

☐ Zusätzliche einstweilige Anmelde-nummern sind im  
Prioritätsanhang aufgeführt.

☐ Additional foreign application numbers are listed  
on a supplemental priority sheet attached hereto.

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated  
below next to my name.

I believe I am the original, first and sole inventor (if only one  
name is listed below) or an original, first and joint inventor (if  
plural names are listed below) of the subject matter which is  
claimed and for which a patent is sought on the invention entitled

GABA UPTAKE INHIBITORS HAVING A PYRROLIDINE  
STRUCTURE

the specification of which is attached hereto unless the following  
box is checked:

☒ was filed on September 3, 1999 as  
United States Application Number \_\_\_\_\_  
and was amended on \_\_\_\_\_ (if applicable)  
or,

PCT International Application Number PCT/EP99/06486  
and was amended on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of  
the above identified specification, including the claims, as  
amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material  
to patentability as defined in Title 37, Code of Federal  
Regulations, § 1.56.

I hereby claim foreign priority under Title 35, United States Code  
§ 119 (a-d) or § 365(b) of any foreign application(s) for patent or  
inventor's certificate, or § 365(a) of any PCT international  
application which designated at least one country other than the  
United States, listed below. I have also identified below, by  
checking the "No" box, any foreign application for patent or  
inventor's certificate, or of any PCT international application  
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priority is claimed:

## German Language Utility or Design Patent Application Declaration

Ich beanspruche hiermit Prioritätsvorteile unter Title 35, US-Code, § 119(e) aller US-Hilfsanmeldungen wie unten aufgezählt.

(Application Number)  
(Aktenzeichen)

(Application Number)  
(Aktenzeichen)

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- ☐ Zusätzliche einstweilige Anmeldeungsnummern sind im ergänzenden Prioritätsanhang aufgeführt.

Ich beanspruche hiermit die mir unter Title 35, US-Code, § 120 zustehenden Vorteile aller unten aufgeführten US-Patentanmeldungen bzw. § 365(c) aller PCT internationalen Anmeldungen, welche die Vereinigten Staaten von Amerika benennen, und erkenne, insofern der Gegenstand eines jeden früheren Anspruchs dieser Patentanmeldung nicht in einer US-Patentanmeldung, bzw. PCT internationalen Anmeldung in in einer gemäß dem ersten Absatz von Title 35, US-Code, § 112 vorgeschriebenen Art und Weise offenbart wurde, meine Pflicht zur Offenbarung jeglicher Informationen an, die zur Prüfung der Patentfähigkeit in Einklang mit Title 37, Code of Federal Regulations, § 1.56 von Belang sind und die im Zeitraum zwischen dem Anmeldetag der früheren Patentanmeldung und dem nationalen oder im Rahmen des Vertrags über die Zusammenarbeit auf dem Gebiet des Patentwesens (PCT) gültigen internationalen Anmeldetags bekannt geworden sind.

(Application No.)  
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(Day/Month/Year Filed)  
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(Application No.)  
(Aktenzeichen)

(Day/Month/Year Filed)  
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I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below.

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(Tag/Monat/Jahr der Anmeldung)

(Day/Month/Year Filed)  
(Tag/Monat/Jahr der Anmeldung)

(Day/Month/Year Filed)  
(Tag/Monat/Jahr der Anmeldung)

- ☐ Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Status)  
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(patentiert, schwebend, aufgegeben)  
(patented, pending, abandoned)

- ☐ Additional U.S. or international application numbers are listed on a supplemental priority sheet attached hereto.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

The undersigned hereby authorizes the U.S. attorney or agent named herein to accept and follow instructions from either his foreign patent agent or corporate representative, if any, as to any action to be taken in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorney or agent and the undersigned. In the event of a change in the persons from whom instructions may be taken, the U.S. attorney or agent named herein will be so notified by the undersigned.

# German Language Utility or Design Patent Application Declaration

**VERTRETUNGSVOLLMACHT:** Als benannter Erfinder beauftrage ich hiermit den sich mit der Kundennummer befassenden Patentanwalt (Patentanwälte) und/oder Patent-Agenten mit der Verfolgung der vorliegenden Patentanmeldung sowie mit der Abwicklung aller damit verbundenen Geschäfte vor dem Patent- und Warenzeichenamt und weise an, dass alle Korrespondenz mit dieser Kundennummer adressiert wird.

**POWER OF ATTORNEY:** As a named inventor, I hereby appoint the attorney(s) and/or agent(s) associated with the Customer Number provided below to prosecute this application and transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

**KUNDENNUMMER 7055**

**CUSTOMER NUMBER 7055**

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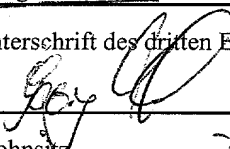
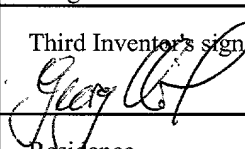



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## German Language Utility or Design Patent Application Declaration

3-00	
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